PEDIATRIC ANTIRETROVIRAL DRUG INFORMATION

Members of the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children have developed this Pediatric Antiretroviral Drug Information Supplement. As new information becomes available, the supplement will be updated. This document contains detailed information about the different classes of antiretroviral agents, and should be used in conjunction with the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (**http://AIDSinfo.nih.gov/**). Dosing information can be found in the **Appendix** to those Guidelines Additionally, antiretroviral drug information updates, labeling changes, and safety warnings may be accessed by subscribing to the U.S. Food and Drug Administration (FDA) HIV/AIDS e-mail list at: **http://www.fda.gov/oashi/aids/email.html.**

Over the last two decades, therapeutic strategies for the treatment of pediatric patients with HIV infection have expanded dramatically from treatment with a single medication to combination therapy that includes up to four different classes of antiretroviral agents. As of September 2005, there were twenty-one antiretroviral agents approved for use in HIV-infected adults and adolescents in the United States; thirteen of these have an approved pediatric treatment indication. These agents are the fusion inhibitors (enfuvirtide*), which prevent viral entry; the nucleoside/nucleotide reverse transcriptase inhibitors (abacavir*, didanosine*, emtricitabine***,** lamivudine*, stavudine*, tenofovir, zalcitabine, and zidovudine*) and non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz*, and nevirapine*), which act at the early stage of replication, prior to viral integration into the host genome; and the protease inhibitors (amprenavir*, atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir*, nelfinavir*, ritonavir*, saquinavir hard- and soft-gel capsules, and tipranavir), which work in the later stage of replication, after viral integration. New antiretroviral agents, such as CCR5 inhibitors, maturation inhibitors, and integrase inhibitors, are currently under investigation.

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*denotes pediatric treatment indication

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

The nucleoside analogue reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral drugs available for the treatment of HIV infection. The NRTIs are potent inhibitors of the HIV reverse transcriptase enzyme, which is responsible for the reverse transcription of viral RNA into DNA; this process occurs prior to integration of viral DNA into the chromosomes of the host cell. The antiviral activity of NRTIs depends upon intracellular serial phosphorylation by host cellular kinases to the active triphosphate drug *[1]*. The phosphorylated drug competitively inhibits viral reverse transcriptase and, following incorporation of the drug into the growing DNA chain, terminates further elongation of viral DNA. Because these drugs act at a pre-integration step in the viral life cycle, they have little to no effect on chronically infected cells, in which proviral DNA has already been integrated into cellular chromosomes. Like the NRTIs, nucleotide reverse transcriptase inhibitors (NtRTIs) also competitively inhibit the viral reverse transcriptase, but because the nucleotide drugs already possess a phosphate molecule (the NRTIs do not), the nucleotide drugs bypass the rate-limiting initial phosphorylation step required for activation of NRTIs.

Although resistance to these agents eventually develops during the course of long-term single drug therapy, combination therapy with these drugs may prevent, delay, or reverse the development of resistance *[2]*. One notable exception is lamivudine (3TC) and emtricitabine (FTC), with which a single point mutation can confer resistance in as little as 4 to 8 weeks when given as monotherapy or in combination with an antiretroviral regimen that does not fully suppress viral replication (e.g., dual NRTI therapy with zidovudine (ZDV)/3TC).

Evidence suggests that polymerase gamma, the DNA polymerase present in mitochondria, is inhibited by NRTIs/NtRTIs *[3-5]*. It is thought that this leads to depletion of mitochondrial DNA (mtDNA) through inhibition of mtDNA synthesis. This depletion may contribute to many of the toxicities associated with NRTIs/NtRTIs. Unusual, but significant, serious toxicities that can occur in patients exposed to these agents include lactic acidosis, hepatic steatosis, pancreatitis, myopathy,

cardiomyopathy, and peripheral neuropathy. Additionally, rapidly ascending muscular weakness has recently been reported as a new symptom of nucleoside analogue-related lactic acidosis and hyperlactatemia. Interestingly, although some toxicities (e.g., lactic acidosis) may occur with all NRTI drugs, other toxicities (such as peripheral neuropathy) may predominantly occur with specific NRTIs, suggesting diverse mitochondrial effects of the drugs that may be dependent on varying ability to penetrate particular cell types. The relative potency of the NRTIs/NtRTIs in inhibiting polymerase gamma *in vitro* is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), and ZDV, with the lowest potency for 3TC, abacavir (ABC), and tenofovir disoproxil fumarate (TDF) *[5, 6]*. The prevalence of mitochondrial-associated adverse effects in children is unknown.

A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC. When using ABC, patients must be cautioned about the risk of serious hypersensitivity reaction and how to recognize symptoms.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have substantial and specific activity against HIV-1, but not HIV-2 or other retroviruses. Unlike the NRTIs, which require intracellular phosphorylation to become active and then cause premature termination of viral DNA synthesis, NNRTIs inhibit HIV DNA polymerase activities by noncompetitively binding to and disrupting a unique catalytic site of the reverse transcriptase enzyme *[7]*. There are currently three NNRTIs approved for the treatment of HIV infection: nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). All members of this class are metabolized by cytochrome P450 (CYP) enzymes, particularly CYP34A, and depending on the agent may induce or inhibit the metabolism of other medications.

NNRTIs rapidly reduce viral load. However, drug resistance develops rapidly after initiation of NNRTI monotherapy or with use in a non-suppressive combination regimen, and cross-resistance readily occurs between the drugs in this class *[8]*. Sustained suppression of viral load has been achieved in patients who have been treated with regimens combining NNRTIs plus NRTIs or NNRTIs plus PIs. A two-dose intrapartum/newborn NVP regimen has been shown to reduce the risk of perinatal HIV transmission by nearly 50% compared to an ultrashort intrapartum/1 week infant ZDV regimen *[9]*.

NNRTIs are associated with several types of hepatic toxicity, including asymptomatic elevation in transaminase levels, clinical hepatitis, and hypersensitivity reaction with hepatitis *[10]*. In HIV-infected adults, risk factors for NVP hepatic toxicity include elevated baseline serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 cell counts (particularly women with CD4 cell counts > 250 cells/mm^3) *[11]*. However, in contrast to what has been reported in adults, serious liver dysfunction appears much less common in pediatric patients receiving NVP therapy *[12]*.

Hypersensitivity reactions are reported more commonly with the NNRTIs than with other antiretroviral agents. EFV can cause adverse CNS effects, including confusion, hallucinations, and nightmares. EFV has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). Use of EFV in the first trimester of pregnancy should be avoided, and before initiating EFV therapy, adult and adolescent women of childbearing potential should undergo pregnancy testing as well as counseling about the risk to a fetus and the need to avoid pregnancy.

Protease Inhibitors

Protease inhibitors (PIs) inhibit the HIV protease enzyme, which is required to cleave viral polyprotein precursors and generate functional viral proteins. The protease enzyme is crucial for the assembly stage of the viral life cycle, which occurs after transcription of proviral DNA to viral RNA and translation of the RNA into viral proteins. Because PIs act at a post-integration step of the viral life cycle, they are effective in inhibiting replication in both newly infected and chronically infected cells *[13]*. The PIs are potent antiretroviral agents, especially when used in combination with NRTI and/or NNRTI therapy *[13]*. Unlike the NRTI drugs, intracellular conversion of the parent compound is not required for activity of any of the protease inhibitors.

Resistance has been reported with all PIs when used as monotherapy, and can develop rapidly even with combination therapy in which drug levels are subtherapeutic (as can occur when there is inadequate dosing, poor drug absorption, rapid drug clearance, or inadequate adherence to the prescribed drug regimen). The patterns of resistance mutations are more complex than observed with the NRTIs and NNRTIs. A larger number of genotypic mutation sites are observed, and there is greater variability in the temporal pattern of development of these mutations and in the combination of mutations that lead to drug resistance. The mutation patterns associated with PI resistance overlap; resistance to one drug may result in reduced susceptibility to some or all of the other currently available PIs.

"Boosted" therapeutic regimens consisting of two PIs (e.g., ritonavir [RTV] plus saquinavir [SQV], amprenavir [APV], fosamprenavir [f-APV], atazanavir [ATV], or indinavir [IDV]) combined with one or two NRTIs are frequently used in adults with good results, especially in PI-experienced patients. However, with the exception of the co-formulated PI lopinavir/ritonavir (LPV/RTV, Kaletra™), there are currently limited data on safety and dosing of combination PI regimens in children.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported in HIV-infected patients treated with any of the currently available PIs *[14-17]*. In some cases, diabetic ketoacidosis has occurred. The PIs have been associated with fat redistribution, lipodystrophy syndrome, and hyperlipidemia in both adults and children *[18]*. A potentially increased risk of cardiovascular disease and of bone disorders, such as osteoporosis and avascular necrosis, are currently being investigated.

Protease inhibitors are metabolized in the liver via the CYP450 enzyme system. A direct human liver microsomal comparison with other PIs showed the following rank order of CYP3A4 inhibition: RTV >> IDV = nelfinavir (NFV) = APV > SQV *[19, 20]*. Clinically significant drug interactions may occur when a PI is administered concomitantly with other agents metabolized by the CYP450 system, especially those metabolized by CYP3A, CYP2D6, CYP2C9, and CYP2C19, and to a lesser extent by CYP2A6, CYP1A2, and CYP2E1. Increased or decreased plasma concentrations of either drug may occur and consequent clinical abnormalities may be seen. See the Pediatric Guidelines **Appendix A: Characteristics of Available Antiretroviral Drugs Matrices 2 – 4** for a list of contraindicated medications. A complete list of potential drug interactions is provided by the PI manufacturer in the prescribing information, which should be consulted prior to initiating PI therapy or starting any new concomitant therapy in patients receiving PI-based regimens.

Fusion Inhibitors

Fusion inhibitors are the newest class of antiretroviral drugs, and act by inhibiting fusion of HIV to target host cells. Enfuvirtide (T-20) is the first drug of the fusion inhibitor class of antiretroviral drugs to be approved; this drug interacts with components of the HIV envelope to prevent fusion of the virus with the host cell membrane. A number of additional inhibitors of viral entry are under study.

Enfuvirtide requires twice daily subcutaneous injections. The high incidence of local injection site reactions (98%) limits the use of the fusion inhibitors in pediatric patients.

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Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen®)

URL:**http://www.fda.gov/cder/foi/label/2000/20978s2lbl.pdf**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
In December 1998, abacavir (ABC) was approved by the FDA for combination therapy in adults and children age 3 months or older, based on controlled trials in adults and children. The combination of ABC, lamivudine (3TC), and zidovudine (ZDV) in a single tablet formulation (Trizivir) for twice daily dosing in adults became available in November 2000. A new formulation combining ABC and 3TC (Epzicom) for administration as a single daily dose for adults was approved in August 2004.

ABC is a guanosine analogue nucleoside reverse transcriptase inhibitor (NRTI). ABC is anabolized intracellularly to carbovir triphosphate by enzymatic pathways distinct from other NRTIs *[1]*. Preliminary studies of carbovir triphosphate suggest persistence in lymphocytes, consistent with single daily ABC dose regimens *[2]*. ABC crosses the blood-brain barrier, with a CSF-to-plasma concentration ratio of 36% *[3]*. Bioavailability is 83%, and mean systemic half-life is 1.5 hours. In humans, cytochrome P450 enzymes do not significantly metabolize ABC, and it in turn does not inhibit human CYP3A4, CYP2D6, or CYP2C activity at clinically relevant concentrations. The primary routes of elimination are metabolism by alcohol dehydrogenase and glucuronyl transferase.

Resistance
ABC resistance mutations have been seen at reverse transcriptase (RT) gene codons K65R, L74V, Y115F, and M184V both *in vitro* and in patients taking ABC *[4, 5]*. At least 2 to 3 mutations are required to reduce susceptibility by 10-fold. Mutations at codons M184V and L74V were most frequently observed in clinical isolates. ABC-resistant virus will be resistant to 3TC. While virus resistant to ZDV or 3TC alone may remain susceptible to ABC, virus resistant to both ZDV and 3TC is more likely to be cross-resistant to ABC. The combination of M184V with ZDV mutations gives rise to high-level ABC resistance *[4]*. While ABC may be included as a component of a treatment regimen for children who have failed prior

antiretroviral therapy, it should be recognized that it is less likely to be active in children with extensive prior treatment with NRTIs. High rates of clinical failure and an accelerated selection of M184V and K65R have been reported when ABC is given in combination with 3TC and tenofovir disoproxil fumarate (TDF) as part of a triple NRTI-only regimen *[6, 7]*.

Adverse Effects
Nausea and vomiting alone may occur in as many as one-third of children receiving ABC in combination with other antiretroviral agents. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ABC.

A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC (see **Matrix 1 in the Appendix**). Symptoms include flu-like symptoms, respiratory symptoms, fever, rash, fatigue, malaise, nausea, vomiting, diarrhea, and abdominal pain. Patients developing these symptoms should have ABC stopped and not restarted, as hypotension and death have occurred with rechallenge. In a randomized study comparing ABC/ZDV/3TC to ZDV/3TC alone, 4 of 146 children receiving ABC and 2 of 44 children receiving ZDV/3TC and who switched to open label ABC therapy developed a hypersensitivity reaction, which resolved upon discontinuation of therapy *[8]*. Onset of the hypersensitivity reaction occurred between 1 to 2 weeks after ABC was started. Some studies have suggested that development of the ABC hypersensitivity reaction may be associated with certain HLA genotypes (e.g., HLA B*5701 genotype) *[9, 10]*; however, HLA genotyping in patients who receive ABC is controversial and its role has yet to be defined *[11, 12]*. When ABC is used, parents and patients must be cautioned about the risk of a serious hypersensitivity reaction; a medication guide and warning card should be provided to parents. Patients should also be advised to consult their physician immediately if signs or symptoms consistent with a hypersensitivity reaction occur. Children experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425).

Pediatric Experience
ABC has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[3, 8, 13-16]*. In the PENTA 5 trial, 130 HIV-infected antiretroviral-naïve children were randomly assigned to one of three different nucleoside analogue regimens: ZDV/3TC, ABC/ZDV, and ABC/3TC, with and without NFV *[14]*. The two ABC-containing regimens were associated with greater mean viral load decreases after 48 weeks of therapy than the ZDV/3TC regimen (-1.71, -2.17, and -2.63 copies/mL with ZDV/3TC, ABC/ZDV, and ABC/3TC, respectively). In this study, 4 children (3%) stopped ABC due to a possible hypersensitivity reaction.

ABC has been studied as part of a protease inhibitor-sparing three-drug NRTI regimen (ZDV, 3TC, and ABC) in antiretroviral-experienced children. In a study of 205 treatment experienced children ranging in age from 0.7 to13 years, the combination of ABC/ZDV/3TC resulted in a greater fall in viral load and increase in CD4 cell count than did ZDV/3TC *[8]*. However, only 10% of 102 children receiving ABC/ZDV/3TC had HIV RNA levels <400 copies/malt 48 weeks of therapy. It is unclear what role triple NRTI combinations may have in the pediatric population. A randomized trial in antiretroviral-naïve adults has shown the combination of ZDV, 3TC, and ABC is virologically inferior when compared to the non-nucleoside reverse transcriptase inhibitor efavirenz combined with 2 to3 NRTI drugs *[17]*. Other trials involving triple NRTI regimens in antiretroviral-naïve adults have also shown decreased virologic potency, raising concern about the routine use of triple NRTI therapies, at least with the currently available drugs *[6, 18, 19]*.

Pharmacokinetic studies of ABC in children less than 12 years of age have demonstrated that pediatric doses approximately twice the adult dose may be necessary to achieve similar systemic exposure *[15]*. Dose regimens for adolescents have not been well studied during chronic therapy, but results from a single-dose pharmacokinetic study suggest that for pediatric patients up to 18 years of age, pharmacokinetic parameters may be more similar to younger children than adults *[16]*. Additional studies on the pharmacokinetics of ABC in adolescents 13 to 24 years of age are ongoing (PACTG 1052). There are no data on once daily dosing of ABC in adolescents.

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Didanosine (ddI, Videx®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Didanosine (ddI) received FDA approval in 1991 for adults and for pediatric patients older than 6 months of age with advanced HIV infection who were intolerant to or deteriorating on ZDV. Since that time, the indications have been broadened and new formulations developed. In October 2000, a new delayed-release formulation of enteric-coated beadlets was approved for use in adults, allowing for once daily ddI administration in selected patients. In December 2004, a generic formulation of ddI delayed-release capsules for once daily administration was approved by the FDA.

ddI is a purine dideoxynucleoside analogue that requires intracellular phosphorylation in resting cells

to become active. Despite lower CSF penetration than ZDV (CSF-to-plasma concentration ratio of 5%), early pediatric studies of ddI monotherapy demonstrated a 46% (range 12 to85%) improvement in neuropsychometric testing scores observed in some children; the improvement was correlated with ddI plasma concentration *[1, 2]*. ddI is unstable at acidic pH and is rapidly degraded unless given as the enteric formulation or combined with buffering agents or antacids. Bioavailability ranges from 20 to 40% depending upon the formulation used. ddI's plasma half-life is 0.5 to 1 hour, but the intracellular half-life of ddI is 25 to 40 hours. The long intracellular half-life allows for the extended dosing interval. Data from PACTG 144 suggest that systemic exposure (i.e., the area under the curve [AUC]) to ddI in children remains similar in the both the presence and absence of food *[3]*. This may allow for the relaxation of fasting state requirement in certain instances.

Resistance
Genotypic mutations at RT gene codons K65R, L74V, and M184V have been associated with ddI resistance. The most common mutation, L74V, is most frequently associated with diminished antiviral activity of ddI. Interestingly, isolates with this resistance mutation have increased susceptibility to ZDV *[4]*. 3TC-resistant virus may have reduced susceptibility to ddI, but cross-resistance is not complete. High rates of clinical failure and an accelerated selection of M184V and K65R have been reported when ddI is given in combination with 3TC and TDF *[5]*.

Adverse Effects
Fatal and nonfatal pancreatitis has occurred during therapy with ddI used alone or in combination regimens in both treatment-naïve and treatment experienced patients, regardless of degree of immunosuppression (see **Matrix 1 in the Appendix**) ddI should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. Pancreatitis appears to be more common in adult patients and may be dose-related. It has occurred more commonly in patients with predisposing factors, including a prior history of pancreatitis, baseline elevation of serum transaminases, and concurrent administration of other drugs known to cause pancreatitis, such as pentamidine and stavudine (d4T) *[6]*. Hydroxyurea appears to increase the risk of pancreatitis when co-administered with ddI; this combination is not recommended.

ddI may cause peripheral sensory neuropathy. Asymptomatic peripheral retinal depigmentation has been observed in <5% of children receiving ddI, is not associated with loss of vision, and appears to reverse with discontinuation of therapy *[7]*. Diarrhea has been reported, and may be more related to the antacid/buffer with which the drug is formulated than to ddI itself. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ddI; the combination of d4T and ddI in pregnant women has been associated with fatal lactic acidosis and should only be used if no other alternatives are available.

Coadministration of TDF with ddI increases peak ddI levels and systemic exposure significantly, and there is an increased risk of ddI-related toxicities when these drugs are administered together *[8-10]*. In addition, ddI in combination with lopinavir/ritonavir (LPV/RTV) and TDF may enhance the nephrotoxic potential of TDF *[11]*. Perhaps because of increased exposure to ddI and resultant lymphocyte toxicity, the combination of ddI plus TDF has been associated with a decline in CD4 cell counts, even when plasma virus load remains low *[12]*. There are no data on coadministration of TDF and ddI in children**.**

Pediatric Experience
ddI has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[2, 3, 13-27]*. Recommended ddI doses in children have traditionally been between 90 to 150 mg per meter^2 body surface area per dose twice daily. Doses higher than 180 mg per meter^2 body surface area are associated with increased toxicity *[2]*. In a simulation based on ddI concentration data from 16 children, a dose of 90 mg per meter^2 body surface area was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared to 88% of patients predicted at a dose of 120 mg per meter^2 *[13]*. This dose of 120 per meter^2 body surface area per dose twice daily has therefore become the "standard" dose of ddI for older infants and children. Data from multiple pediatric studies of ddI alone or in combination with other drugs, including a study of long-term ddI use (median duration of almost 2 years), show that ddI appears safe and is associated with clinical improvement, increase in CD4 count, and decrease in viral load *[14-19, 28]*.

Three major areas of controversy remain in the use of ddI in the treatment of children with HIV infection: 1) the appropriate dose to use in infants 2 weeks to 4 months of age; 2) the need to dose ddI on an empty stomach; and 3) the potential use of enteric-coated ddI (Videx EC) once daily in children.

The "usual pediatric dose" of 120 mg per meter^2 body surface area per dose twice daily was used successfully in combination therapy in infants 2 to 16 months of age, without significant toxicity *[20]*. Currently, the FDA recommends 100 mg per meter^2 body surface area per dose twice daily for infants from 2 weeks to 8 months of age, increasing to 120 mg per meter^2 body surface area per dose twice daily at age 8 months. However, two small studies suggest that higher AUCs are seen in infants under 6 weeks of age, and that a dose of 100 mg per meter^2 body surface area per day (either as 50 mg per meter^2 per dose twice daily or 100 mg per meter^2 body surface area once daily) achieves AUCs consistent with those of higher doses in older children *[21, 22]*. Therefore, because of pharmacokinetic differences in younger infants (2 weeks to 4 months) compared to older children, a dose of 50 mg per m^2 of body surface area twice daily may be more appropriate in younger infants.

While the prescribing information recommends taking ddI on an empty stomach, this is impractical for infants who feed frequently, and may decrease medication compliance by increasing regimen complexity. A comparison of ddI given with or without food in children found that systemic exposure was similar, but with slower and more prolonged absorption *[3]*. To improve compliance, some practitioners recommend administration without regard to timing of meals for young children. However, there are inadequate data to allow a strong recommendation at this time, and it is preferred that ddI be administered under fasting conditions when possible.

Enteric-coated ddI (Videx EC) administered as a single dose of 240 mg per meter^2 body surface area has been shown to have similar plasma AUC (although lower peak plasma levels) compared to the equivalent dose of buffered ddI *[23]*. The resultant intracellular (active) drug concentrations are unknown. In 24 children with HIV infection, ddI at a dose of 180 mg per meter^2 body surface area once daily was compared to 90 mg per meter^2 body surface area twice daily, and the AUC was actually higher in the once daily group than in the twice daily group *[24]*. In fact, in 53 children with advanced symptomatic HIV infection, once versus twice daily ddI at a dose of 270 mg per meter^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was poorer in the children given once daily therapy *[25]*. Currently Videx EC is FDA approved only for persons over 18 years of age.

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Emtricitabine (FTC, Emtriva™)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

See Also: Appendix: Characteristics of Available Antiretroviral Drugs

Overview

Emtricitabine (FTC) was approved in July 2003 for treatment of HIV infection in adults aged 18 years or older and in September 2005 for treatment in children aged 3 months to 17 years. A fixed-dose combination formulation of FTC and TDF (Truvada) was approved for adult patients in 2004. Safety and effectiveness of FTC in pediatric patients is under study.

FTC is a synthetic cytosine nucleoside analogue (2'deoxycytidine). It differs only slightly in structure from 3TC (5-fluoro substitution), although its potency is on average five times higher in *in vitro* tests against HIV strains from primary clinical

isolates *[1, 2]*, and it may be more effective *in vivo* as well *[3]*. Concentrations required for 50% inhibition of HIV-1 are 10 to 20 nanomoles/L. Like other NRTI drugs, FTC requires intracellular phosphorylation to become active. FTC is metabolized intracellularly and its primary route of elimination is via renal excretion without significant metabolic interactions with other antiretroviral drugs.

FTC is well absorbed rapidly following oral administration. Systemic exposure (AUC) is unaffected by administration of FTC with food. FTC pharmacokinetics are linear over a wide dosage range. The terminal half-life of FTC in plasma is 8 to10 hours.

Limited data suggest FTC, like 3TC, is active against hepatitis B virus, although the safety and efficacy of FTC in HIV-infected patients co-infected with hepatitis B has not been established. "Flare-ups" of hepatitis B have been reported in HIV/hepatitis B co-infected patients after discontinuation of FTC therapy. Co-infected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping FTC treatment.

Resistance
Like 3TC, resistance to FTC is associated with a single genotypic mutation at RT gene codon 184. FTC-resistant isolates are cross-resistant to 3TC and ddC, but retain sensitivity to ABC, ddI, d4T, TDF, ZDV, and NNRTI drugs. In fact, the M184V mutation enhances HIV susceptibility to TDF *[4]*. HIV-1 isolates containing the K65R mutation, selected in vivo by ABC, ddI, TDF, and ddC, have reduced susceptibility to FTC. In-vitro data have shown that resistance to 3TC confers cross-resistance to FTC.

Adverse Effects
FTC is well tolerated. The most common adverse events reported in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity and required drug discontinuation in only 1% of patients. Skin discoloration, manifested by hyperpigmentation of the palms and/or soles, has been observed, predominantly in non-Caucasian patients. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including FTC (see **Matrix 1 in the Appendix**).

Pediatric Experience
FTC has been studied in HIV-infected children in combination with ddI/EFV and d4T/LPV/RTV *[5-7]*. A single-dose pharmacokinetic study of FTC liquid solution and capsules was performed in 23 HIV-infected children 2 to17 years of age *[5]*. FTC was found to be well-absorbed following oral administration, with a mean elimination half-life of 11 hours (range 9.7 to11.6 hours). Based on this dose-finding study, FTC was given at a dose of 6 mg/kg once daily in combination with other antiretroviral drugs in a phase II study in 82 HIV-infected children *[6]*. Antiretroviral-naïve children received FTC plus d4T and LPV/RTV. Treatment experienced children were maintained on their initial regimen, but changed from 3TC to FTC. Plasma concentrations in children receiving the 6 mg/kg FTC once daily dose are approximately equivalent to those in adults receiving the standard 200 mg dose, although younger children (under 2 years of age) may have more rapid absorption and more rapid clearance, resulting in lower trough levels *[6]*. FTC at a dose of 6 mg/kg (maximum 200 mg/day) in combination with ddI and EFV, all given once daily, is under study in antiretroviral-naïve HIV-infected children aged 3 months to 21 years. This regimen has been well tolerated and FTC and ddI concentrations have met the desired target study concentrations *[7]*.

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Lamivudine (3TC, Epivir®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview

Lamivudine (3TC) was approved in November 1995 for use in children and infants greater than 3 months of age based on efficacy studies in adults in conjunction with safety and pharmacokinetic studies in children. In September 1997, it was approved as a fixed combination of 3TC/ZDV (Combivir) for adults and adolescents greater than 12 years old. In November 2000, it was approved as a fixed-dose combination of 3TC/ZDV/ABC (Trizivir) for adolescents and adults weighing greater than 40 kg. In August 2004, it was approved as a fixed-dose combination of 3TC /ABC (Epzicom) for once daily dosing in adults.

3TC is the negative enantiomer of a synthetic cytidine analogue. 3TC requires intracellular phosphorylation to become active and, like ddI and ddC, does so preferentially in resting cells. 3TC has activity against HIV-1, HIV-2, and hepatitis B virus. The CSF-to-plasma concentration ratio in children is relatively low (0.11) compared with that of ZDV (0.25), but higher than that of ddI (0.05) *[1]*. The bioavailability is approximately 66% in children and 86% in adolescents and adults. Its plasma half-life is 2 hours and its intracellular half-life is 10 to15 hours, allowing for twice daily dosing in children and once daily dosing in adults.

3TC is active against hepatitis B virus, and "flare-ups" of hepatitis B have been reported in HIV/hepatitis B co-infected patients after discontinuation of 3TC therapy. Co-infected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping 3TC treatment.

Resistance

When 3TC is administered as monotherapy, resistance emerges rapidly and is associated with a single genotypic mutation at RT gene codon 184. Resistance also develops rapidly (within weeks) when 3TC is used in non-suppressive combination antiretroviral regimens, such as dual NRTI therapy with ZDV/3TC *[2]*. Therefore, optimal use of 3TC is in a combination of at least three antiretroviral medications capable of providing full suppression of viral replication. 3TC-resistant virus may be partially cross-resistant to ddI and ddC. *In vitro*, development of the codon 184 mutation is associated with increased fidelity of the viral reverse transcriptase enzyme for its substrate *[3]*. It is speculated that this could influence the evolution of the virus and may prevent or delay the generation of drug resistant variants. For example, the 184 mutation is reported to suppress ZDV resistance *in vitro*; when introduced into the background of a ZDV-resistant RT gene, the 184 mutation suppresses the effect of some ZDV resistance mutations *[4]*. Additionally, the M184I/V mutation is associated with diminished viral replicative fitness *[5]*.

Adverse Effects

3TC is very well tolerated. The major reported toxicities are pancreatitis and peripheral neuropathy *[1]*. Headache, fatigue, and gastrointestinal upset have also been described. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including 3TC (see **Matrix 1 in the Appendix**).

Pediatric Experience

3TC has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[1, 6-15]*. Data from multiple pediatric studies of 3TC alone or in combination with other drugs demonstrate that 3TC appears safe and is associated with clinical improvement and virologic response *[1, 6-8]*. 3TC is commonly used in HIV-infected children as a component of a dual NRTI backbone (most often with ZDV or d4T) used as part of a highly active antiretroviral therapy regimen.

Little data are available regarding once daily administration of 3TC in children. The pharmacokinetics of once daily vs twice daily dosing of 3TC (8 mg/kg once daily vs 4 mg/kg twice daily) and ABC (16 mg/kg once daily vs 8 mg/kg twice daily) were evaluated in 20 HIV-infected

children aged 2 to 13 years; the AUC_{0-24} for both drugs was similar with once and twice daily administration, and no major toxicities were noted *[9]*. At this time, once daily dosing of 3TC is only recommended for adolescents ≥16 years and ≥50 kg.

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Stavudine (d4T, Zerit®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview

Stavudine (d4T) was approved in September 1996 for use in infants and children greater than six months of age based on evidence from controlled trials in adults and on safety and pharmacokinetic data from children.

d4T, like ZDV, is a thymidine analogue. It is preferentially phosphorylated and exerts more potent antiviral activity in activated rather than in resting cells. CSF concentrations of d4T varied widely (16 to 97% of plasma concentrations) in a study of eight pediatric patients receiving chronic dosing *[1]*. Drug absorption is reliable, with bioavailability greater

than 80%. The plasma half-life in adults is 1.4 hours and the intracellular half-life is 3.5 hours. In pediatric patients, the plasma half-life is 0.96 hours. ZDV is a potent inhibitor of the intracellular phosphorylation of d4T *in vitro*, and at least one adult clinical trial indicates that there may also be *in vivo* antagonism associated with this combination *[2, 3]*. Therefore, d4T and ZDV should not be co-administered.

Resistance
High-level resistance to d4T has been difficult to demonstrate; genotypic mutations at RT gene codons 50 and 75 appear to be associated with diminished *in vitro* susceptibility to d4T. Emergence of genotypic mutations associated with ZDV resistance in ZDV-naïve individuals receiving therapy with d4T-based regimens has been reported *[4]*. Susceptibility to d4T (as well as to ZDV and TDF) may be enhanced in the presence of the M184V mutation in the RT gene, even if there is a single thymidine analogue mutation that would usually decrease d4T susceptibility *[5]*.

Adverse Effects
One of the most significant toxicities associated with d4T is peripheral neuropathy, but this appears to be less common in children than in adults *[1, 6]*. Elevated hepatic transaminases are seen in about 11% and pancreatitis in 1% of adults enrolled in clinical trials of d4T. d4T has been studied in pediatric patients in combination with ddI; no pharmacokinetic interactions were observed and there were no cases of peripheral neuropathy *[7]*. Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with the use of NRTIs, particularly d4T, in adults and children *[8, 9]*. The incidence of lipoatrophy associated with d4T use in children is unknown, and further research concerning body habitus changes associated with NRTI use in pediatric patients is ongoing. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including d4T; the combination of d4T and ddI in pregnant women has been associated with fatal lactic acidosis and should be used only if no other alternatives are available (see **Matrix 1 in the Appendix**).

Pediatric Experience
d4T has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[1, 6, 7, 10-15]*. Data from multiple pediatric studies of d4T alone or in combination with other antiretrovirals demonstrate that d4T appears safe and is associated with clinical and virologic response *[1, 6, 7, 10-13]*. In HIV-infected children, d4T is commonly used as a component of a dual NRTI backbone (most often with 3TC or ddI) used as part of a highly active antiretroviral therapy regimen.

Many clinicians use d4T as a replacement for ZDV when combination drug regimens are changed; in a phase II comparison study of d4T and ZDV, they were largely comparable in terms of safety and tolerability, although neutropenia occurred significantly less often among children receiving d4T *[6]*.

Early initiation of triple therapy including d4T, ddI, and nelfinavir (NFV) was evaluated in 20 infants starting therapy at <3 months of age (median age at initiation, 2.5 months) *[13]*. Therapy was generally well tolerated; 7 infants (35%) experienced 11 events considered possibly related to study drugs, although only 3 such events required drug modification (these 3 events were rash, diarrhea, and neutropenia. At least one episode of grade 1 hypertriglyceridemia was observed in 19 of 20 (95%) infants; 9 of 12 (75%) infants with cholesterol measured after baseline had at least one episode of grade 1 hypercholesterolemia. However, no infant had grade 2 or higher triglyceride or cholesterol levels. 70% of infants had incomplete viral suppression, which was associated with genotypic resistance mutations in 6 (30%) of these infants. However, only two infants developed resistance mutations to d4T, and one of these infants had pre-existing thymidine analogue resistance mutations present at baseline.

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Tenofovir Disoproxil Fumarate (Viread®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Tenofovir disoproxil fumarate (TDF) was approved for use in combination with other antiretroviral agents for treatment of adults in October 2001. A fixed dose combination formulation of TDF and FTC (Truvada) was approved for adults in August 2004. TDF is not approved for use in pediatric patients <18 years old.

Tenofovir is an acyclic nucleotide analogue with activity against retroviruses, including HIV-1 and HIV-2, and hepatitis B virus. TDF, an orally active ester prodrug of tenofovir, is rapidly hydrolyzed to tenofovir by plasma esterases, then metabolized intracellularly to the active drug, tenofovir diphosphate, which competitively inhibits the HIV RT enzyme and terminates the DNA synthesis. The drug has a long half-life, allowing once daily dosing in adults, and is active against many viruses resistant to NRTIs, NNRTIs, and PIs. Oral bioavailability in adults ranges from 25% (fasting) to 39% (after a high-fat meal). TDF can be taken with or without food. TDF is excreted unchanged by the kidneys by a combination of glomerular filtration and active tubular secretion, and the dose should be adjusted for patients with renal insufficiency. There is potential for interaction with other drugs that undergo renal excretion. There is no hepatic metabolism of TDF, and pharmacokinetics are unchanged in patients with hepatic impairment.

TDF is active against hepatitis B virus, and “flare-ups” of hepatitis B have been reported in HIV/hepatitis B co-infected patients after discontinuation of TDF therapy. Co-infected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping TDF treatment.

Resistance
While tenofovir is active against viral strains that are resistant to other drugs, HIV isolates with reduced susceptibility to tenofovir have been selected *in vitro*; these viruses expressed a K65R mutation in the RT gene and have a 3 to 4-fold reduction in susceptibility to TDF. The K65R mutation can also be selected *in vivo* in patients receiving ddI, ddC, or ABC; thus, patients who develop the K65R mutation following treatment with ddI, ddC, or ABC may have some cross-resistance to TDF. Viruses containing multiple thymidine analogue mutations (e.g., mutations at RT gene codons 41 and 210, which also confer resistance to d4T, ZDV, and ABC), a mutation at codon 74 (which confers resistance to ABC, ddI, and ddC), or the T69S double insertion resistance mutation also have reduced susceptibility to TDF.

Adverse Effects
In animal studies, the principal organs affected by TDF toxicity were the renal tubular epithelium and bone. Evidence of reversible renal toxicity, including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and calciuria and decreases in serum phosphate (Fanconi Syndrome), has been observed in animal studies at high exposure levels; however, toxicity was not observed in infant macaques treated with low-dose tenofovir for five years *[1]*. Although TDF-associated renal toxicity has been observed infrequently in clinical studies of adults *[2, 3]*, there are now numerous case reports of nephrotoxicity (Fanconi Syndrome, renal insufficiency, acute tubular necrosis, acute renal failure) in adults receiving TDF in combination with other drugs *[2, 4-9]*. There is greater risk for patients with low body weight, baseline renal insufficiency, and those using concomitant drugs that are nephrotoxic or increase the patient's TDF exposure. Discontinuation of TDF led to improvement or resolution of these clinical abnormalities. The long-term renal effects are not known. Unpublished cases of renal toxicity in adolescents taking TDF-containing regimens support the need to evaluate and monitor renal function in patients using TDF, regardless of age.

Tenofovir caused bone toxicity (osteomalacia, growth restriction) in infant macaques when given in high-doses over long periods *[1]*. This was reversed with dose reduction or complete discontinuation of tenofovir. Infant macaques receiving low daily doses of tenofovir for five years experienced normal growth and bone density *[1]*. Decreases in bone mineral density (BMD) have been shown in both adults and children taking TDF for 48 weeks *[10]*. The clinical significance of changes in BMD is not yet known; no increase in fracture incidence has been observed.

There is a poorly understood drug-drug interaction between tenofovir and ddI that results in significantly increased ddI levels and increased ddI toxicity. When co-administering ddI and TDF, a dose adjustment of ddI is recommended (the exact dose adjustment needed in children, however, is not known); patients should be monitored for symptoms of ddI toxicity, lymphopenia, and declining CD4 cell counts *[4, 11]*. ATV and LPV/RTV increase TDF concentrations. The mechanism of this interaction is not known. Patients receiving ATV or LPV/RTV in combination with TDF should be monitored closely for TDF-associated adverse effects, and TDF should be discontinued if they occur. TDF decreases concentrations of ATV.

TDF appears less likely than other NRTI drugs to be associated with mitochondrial toxicity *[12, 13]*; TDF inhibits HIV reverse transcriptase at concentrations about 3,000-fold lower than needed to inhibit DNA polymerases beta and gamma, and is also only a weak inhibitor of the alpha, beta, and gamma DNA polymerases. In adult studies, the rate of mitochondrial side effects was 3% among TDF recipients, compared to 11% among those taking d4T *[14]*. However, cases of lactic acidosis have been reported with use of TDF *[4, 15]* (see **Matrix 1 in the Appendix**).

Pediatric Experience
TDF has been studied in HIV-infected children in combination with other NRTIs *[10, 16-18]*. Antiretroviral activity of TDF-containing combinations has been demonstrated through 48 weeks in heavily treatment experienced children and adolescents *[16]*. Single-dose and steady-state pharmacokinetics of a 75 mg tablet formulation of TDF have been evaluated in treatment experienced children and adolescents ages 6 to18 years *[17]*. A daily dose of 175 mg/m2 (median dose 208 mg per meter^2 of body surface area, range 161 to 256 mg per meter^2 body surface area) approached TDF drug exposure similar to that seen in adults using a daily dose of 300 mg. Mean single dose AUC and C_{max} were 34% and 27% lower, respectively, compared to values reported in adults *[17, 19]*. Renal clearance of TDF was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure *[17]*.

A phase II study evaluated the clinical response to TDF given with optimized antiretroviral regimens in 19 children aged 6 to16 years with extensive prior antiretroviral experience. Median decrease in $\log_{10}$ HIV RNA was 0.53 at 24 weeks and 1.52 at 48 weeks. RNA was < 400 copies/mL in 6 subjects and < 50 copies/mL in 4 subjects at each time point *[16]*. BMD measured by dual-energy x-ray absorptiometry (DEXA) scan was also evaluated. Baseline lumbar bone density was at least 1 standard deviation below the norm, indicating a high prevalence of osteopenia prior to receiving TDF. BMD decreased after 24 weeks of TDF therapy, but appeared to stabilize despite continued treatment from 24 to 48 weeks *[10]*. Height and weight z-scores were also below normal at baseline and appeared to improve at 48 weeks, suggesting no short-term risk to growth. No BMD studies have been performed in treatment-naïve children.

An investigational liquid formulation has been studied in children age 2 to 8 years; a TDF dose of 8 mg/kg resulted in TDF exposure similar to that observed in adults receiving a TDF 300 mg dose *[18]*.

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Zalcitabine (ddC, Hivid®)

URL:**http://www.rocheusa.com/products/hivid/pi.html**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
In June 1992 zalcitabine (ddC) was approved for use in adults and adolescents older than 13 years of age. It is not FDA-approved for use in pediatric patients.

ddC is a cytidine analogue that undergoes intracellular phosphorylation to its active form in resting cells. It is well absorbed from the gut, with approximately 70 to 80% bioavailability in adults. Absorption is reduced by administration with food. The plasma half-life in HIV-infected adults ranges from 1 to 3 hours, and the intracellular half-life is approximately 2.6 hours. There are limited pharmacokinetic data in children. Oral bioavailability in children is approximately 54%, compared with almost 90% in adults. In a limited study of children ranging in age from 6 months to 13 years, the plasma half-life was 0.2-1.9 hours.

Resistance
Genotypic mutations at RT gene codons 65, 74, 75, 69, 184, and 215 are associated with ddC resistance. The multi-nucleoside analogue resistance complex of mutations occurring together at codons 62, 75, 77, 116, and 151 is associated with high-level ddC resistance as well as resistance to all the nucleoside analogue reverse transcriptase inhibitors.

Adverse Effects
Although uncommon in children, peripheral neuropathy was observed in a pediatric trial of ddC *[1]*. Peripheral neuropathy has been reported in up to a third of adults with advanced HIV disease. ddC has toxicities similar to ddI and d4T; combination with ddI or d4T is not recommended due to overlapping genotypic resistance mutations and enhanced risks of peripheral neuropathy and pancreatitis. Rashes and oral ulcerations have also been reported with ddC therapy in children *[2]*. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ddC (see **Matrix 1 in the Appendix**). Rare cases of hepatic failure and death have been reported in adults with underlying hepatitis B infection.

Pediatric Experience
ddC has been studied in HIV-infected children as monotherapy and in combination with other NRTIs *[1-6]*. Data from multiple pediatric studies of ddC alone or in combination with other antiretrovirals demonstrate that ddC appears safe and is associated with clinical improvement and virologic and immunologic effects *[1-6]*. However, ddC is infrequently used in pediatric patients because it offers no advantages over the other NRTIs, may be associated with a higher incidence of neuropathy, and is not available as a pediatric formulation.

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Zidovudine (ZDV, AZT, Retrovir®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Zidovudine (ZDV) was the first NRTI studied in adult and pediatric clinical trials and the first antiretroviral agent approved for treatment of HIV infection. ZDV first received FDA approval for the treatment of HIV infection in adults in 1987. It was approved for use in children ages 3 months to 12 years in May 1990. In September 1997, it was approved as a fixed combination of ZDV/3TC (Combivir) for adults and adolescents greater than 12 years old. In November 2000, it was approved as a fixed-dose combination of ZDV/3TC/ABC (Trizivir) for adolescents and adults weighing greater than 40 kg. In September 2005, a generic oral formulation of ZDV was approved by the FDA for pediatric use; generic ZDV tablet formulations were also approved. Perinatal trial PACTG 076 established that a ZDV prophylactic regimen given during pregnancy, labor, and to the newborn reduced the risk of perinatal HIV transmission by nearly 70% *[1]*. ZDV received FDA approval for that indication in August 1994.

ZDV is a thymidine analogue that has its greatest activity in replicating cells. It has good CNS penetration (CSF-to-plasma concentration ratio = 0.68) and is the NRTI of choice when treating children with HIV-related CNS disease *[2]*. ZDV is metabolized by the liver, primarily by glucuronidation, and then excreted by the kidneys. It is well absorbed in the gut, with an average bioavailability of approximately 60%, and is approximately 35% protein bound. ZDV requires intracellular phosphorylation to become activated. The serum half-life is 1.1 hours and the intracellular half-life is 3 hours.

Resistance
The antiretroviral activity of ZDV as monotherapy is limited by emergence of resistance, which generally occurs after months to years of treatment, depending on the patient's disease stage *[3]*. ZDV resistance is a consequence of a stepwise accumulation of genotypic mutations in the viral RT enzyme, including substitutions at RT gene codons 41, 67, 70, , 210, 215, and 219. The quantity and pattern of mutations influence the level of phenotypic resistance. The codon 184 mutation associated with 3TC resistance is reported to suppress ZDV resistance *in vitro;* when introduced into the background of a virus containing a ZDV-resistant reverse transcriptase gene this mutation suppresses the effect of some ZDV resistance mutations *[4, 5]*. A small proportion of patients taking ZDV may develop a multi-drug resistance genotype, leading to cross-resistance to all NRTI drugs *[6]*.

Adverse Effects
ZDV is generally well tolerated in children; the major toxicities are macrocytic anemia and neutropenia *[7]*. Dose reduction and hematopoietic growth factors such as erythropoietin and filgrastim (G-CSF) have been used to mitigate these toxicities. ZDV has also been associated with reversible myopathy and cardiomyopathy. Other reported toxicities of ZDV include fatigue, headache, and nausea. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ZDV (see **Matrix 1 in the Appendix**).

Pediatric Experience
ZDV has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[2, 7-20]*. Data from multiple pediatric studies of ZDV alone or in combination with other antiretrovirals demonstrate that ZDV appears safe and is associated with clinical improvement and virologic and immunologic effects *[7-13]*. ZDV is commonly used in HIV-infected children as a component of a dual NRTI backbone (most often with 3TC, ddI, or ABC) used as part of a highly active antiretroviral therapy regimen.

Recommended neonatal ZDV dosing is 2 mg/kg orally every 6 hours or 1.5 mg/kg intravenously every 6 hours for those unable to receive oral dosing. Pharmacokinetic studies, such as PACTG 331, have shown that dose adjustments are necessary for premature infants due to decreased ZDV clearance compared to term newborns of similar postnatal ages *[14, 15]*. Overall, ZDV pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. The manufacturer's recommended oral dose in pediatric patients 6 weeks to 12 years of age is 160 mg per meter^2 of body surface area every 8 hours, in combination with other antiretroviral agents, while the recommended dose for adults is 300 mg twice daily. Due to the possible clinical benefit of improved medication adherence expected with twice

daily drug regimens, many pediatric investigators and clinical experts suggest an oral dose of 180 to 240 mg per meter^2 of body surface area twice daily in children and adolescents *[8, 21]*. However, pharmacokinetic data supporting twice daily dosing in children is absent.

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Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

Delavirdine (DLV, Rescriptor®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Delavirdine (DLV) was approved in April 1997 for use in adults and adolescents 16 years and older in combination with other antiretroviral agents. This agent, like others in its class, is specific for HIV-1 and has no activity against HIV-2. This NNRTI has had very limited study in pediatric patients under 13 years.

DLV is metabolized in part by the hepatic cytochrome P450 3A (CYP3A) enzyme system. In general, DLV is considered an inhibitor of these cytochrome P450 isoenzymes and may decrease the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Because of its ability to delay clearance of some protease inhibitors, DLV is considered for use in combination with amprenavir (APV), indinavir (IDV), and saquinavir (SQV) to increase trough plasma concentrations of those agents. However, concerns about NNRTI cross-resistance may limit the utility of such combinations, and they are not currently recommended.

Resistance
As with the other NNRTIs, DLV resistance can be induced by a single point mutation. DLV has primary resistance mutations at RT gene codons 103 and 181, so resistance to DLV predicts resistance to NVP and EFV. The highest degree of resistance to DLV, however, is found with a combination of mutations at codons 181 and 236.

Adverse Effects
As with the other NNRTIs, skin rash is the most common toxicity observed with DLV. Skin rash attributable to DLV was observed in 18% of all adults receiving combination regimens with DLV in phase II and III trials; an incidence rate as high as 50% was reported in some trials *[1]*. Dose titration did not significantly reduce the incidence of rash, but the rash was more common in adults with lower CD4 cell counts and typically appeared within one to three weeks of treatment. While rare, severe rash, such as Stevens-Johnson syndrome, does occur; as with the other NNRTIs, DLV should be discontinued if severe rash or severe rash with constitutional findings occurs. Other toxicities were uncommon. Elevated liver transaminases were observed in 2 to 7% of adults receiving DLV, but did not differ from comparison groups receiving regimens not including DLV. In the one phase I study involving children, the most frequently reported adverse effects were rash in 40% (all grade 1 or 2) and vomiting in 40% *[1, 2]*.

Pediatric Experience
DLV has been studied in HIV-infected children as monotherapy and in combination with amprenavir (APV) *[2-4]*. DLV was evaluated in one phase I study in 15 children aged 5 months to 15 years and in one small combination therapy pharmacokinetic study in 6 children aged 5 to 18 years old *[3]*. DLV was administered twice daily as an oral suspension or as a tablet or tablet dispersion at doses ranging from 12 to28 mg/kg body weight *[2]*. Doses of 16 mg/kg twice daily in children 5 months or older produced systemic DLV exposure similar to that achieved in adults receiving doses of 400 mg three times daily. When combined with APV, a higher twice daily dose of DLV was required *[3]*, No other pediatric studies are available at this time. DLV is infrequently used in pediatric patients because it offers no advantages over the other NNRTIs, requires three times a day dosing, has limited pediatric experience, and is not available as a pediatric formulation. Additionally, it is only approved in children older than 16 years of age.

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Efavirenz (DMP-266, EFV, Sustiva™)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Efavirenz (EFV) was approved in September 1998 for adults, adolescents, and children older than 3 years of age. Like the protease inhibitors, EFV is metabolized via the cytochrome P450 pathway (primarily CYP3A4 and CYP2B6). EFV has been shown to induce its own metabolism and to be a mixed inducer/inhibitor of cytochrome P450 isoenzymes. Therefore, concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. In addition, concomitantly administered medications that induce or inhibit cytochrome P450 isoenzymes may affect the plasma concentrations of EFV. EFV is highly protein bound (>99%), and may therefore interact with other highly protein bound drugs, such as phenobarbital and phenytoin.

Resistance
EFV, like other NNRTIs, has a low genetic barrier to resistance, with high-level resistance seen with a single mutation (lysine to asparagine), typically RT gene codon 103. Other known mutations conferring phenotypic resistance include those at codons 100, 108, or 225. Cross-resistance to EFV is likely with DLV-resistant virus and in some cases with NVP-resistant virus; the extent of cross-resistance varies depending on which genotypic mutations are present.

Adverse Effects
The toxicity profile for EFV differs for adults and children. In adults, a CNS complex of confusion, agitation, sleep disturbance, nightmares, hallucinations, or other symptoms has been reported in more than 50% of patients *[1]*. These symptoms usually occur early in treatment and rarely require drug discontinuation. Bedtime dosing, particularly during the first several weeks of therapy, appears to decrease the occurrence and severity of this side effect. Adverse CNS effects occurred in 14% of children receiving EFV in clinical studies *[2]*. The principal side effect of EFV in children is rash, which was seen in up to 40% of children, compared to 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically in the first 2 weeks of treatment *[2]*. While severe rash and Stevens-Johnson syndrome have been reported, this is rare. Other reported adverse events in adults and children include diarrhea, nausea, and increased aminotransferase levels.

In cynomolgus monkeys, prenatal EFV exposure has been associated with congenital CNS abnormalities in infant monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in four infants after first trimester exposure to EFV-containing regimens (3 meningomyeloceles and 1 Dandy-Walker malformation), EFV has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). EFV use in the first trimester of pregnancy should be avoided, and adult and adolescent women of childbearing potential should undergo pregnancy testing as well as counseling about the risk to the fetus and the need to avoid pregnancy before initiating EFV therapy (see **Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States** *[3]*.

Pediatric Experience
EFV has been studied in HIV-infected children in combination with NRTIs or with NRTIs and a PI (nelfinavir [NFV] or lopinavir/ritonavir [LPV/RTV]) *[2, 4-11]*. An open label study (PACTG 382) of EFV combined with NFV and one or two NRTIs was performed in 57 NNRTI- and PI-naïve pediatric patients, some as young as age 3 years *[2]*. In an intent-to-treat analysis, 76% of children had plasma HIV RNA levels <400 copies/mL and 63% had HIV RNA levels <50 copies/mL at 48 weeks of therapy. The median times to achieve those levels were 4 and 20 weeks, respectively. Therefore, children with detectable HIV RNA (greater than 50 copies/mL by the ultra-sensitive RNA assay) after one month of therapy continued to accrue some virologic benefit through 5 months of treatment with this regimen *[4]*.

A study of a liquid formulation of EFV in 19 HIV-infected children aged 3 to 9 years of age has been reported *[5]*. Studies in adult volunteers indicated that bioavailability of EFV liquid is 20% lower than that of the capsules; therefore, the initial dose of EFV liquid formulation was 20% higher than that used for EFV capsules in the earlier pediatric study (PACTG 382). The higher dose of EFV liquid formulation resulted in pharmacokinetic AUC values that were similar to those observed with EFV

capsules. Antiviral effects were similar in children receiving either the liquid or the capsule EFV formulation. Pharmacokinetic data are not yet available for dosing in children under the age of 3 years or who weigh less than 13 kg. The liquid form of EFV is not yet commercially available.

EFV should be used with caution in adolescent women of childbearing age because of the risk for teratogenicity should EFV be taken during the first trimester, prior to recognition of pregnancy. Some clinicians may choose alternative drugs for use in sexually active adolescent women in whom contraception is erratic and the risk of unintended pregnancy is high.

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Nevirapine (NVP, Viramune®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Nevirapine (NVP) is approved for use in children greater than 2 months old. NVP is a dipyridodiazepinone derivative NNRTI that binds directly to the HIV-1 reverse transcriptase enzyme; reverse transcriptase inhibition is specific to HIV-1, and the drug has no activity against other retroviruses, including HIV-2. NVP does not inhibit any of the human cellular DNA polymerases.

NVP is highly lipophilic and widely distributed in the body; CSF- to-plasma concentration ratio is approximately 0.45. NVP undergoes extensive hepatic metabolism by way of hepatic cytochrome P450 metabolic enzymes, which NVP itself induces. During the course of the first 2 weeks of administration, plasma clearance increases as half-life decreases. NVP clearance in children is greater than in adults, and clearance in children under 9 years of age is greater than in older children *[1]*. Due to induction of cytochrome P450 hepatic enzymes, concomitantly administered medications that induce or inhibit cytochrome P450 enzymes may affect the plasma concentration of NVP. Medications that undergo hepatic metabolism by cytochrome P450 enzymes may have levels increased or decreased by concomitant NVP administration.

Resistance
NVP has potent antiviral activity, but drug resistance develops rapidly when NVP is administered as monotherapy *[2, 3]*. High-level resistance has been associated with a single point mutation at codon 103, 106, 108, 181, or 188 in the RT gene, with a

mutation at codon 181 being the most common *[4, 5]*. Mutations associated with resistance to NVP can confer cross-resistance to other NNRTIs. HIV subtype B viruses that contain the K103N mutation as opposed to the Y181C mutation may differ in their cross-resistance to EFV *[6, 7]*. Viruses with the Y181C mutation alone have little resistance to EFV (although Y181C can enhance the level of resistance of viruses containing additional NVP mutations), whereas viruses with the single K103N mutation are cross-resistant to other NNRTIs *[8]*. Genotypic mutations associated with viral resistance to NVP typically occur within one to six weeks after initiation of NVP in situations where viral production is not effectively controlled *[2, 3]*. With the exception of the use of the two-dose intrapartum/newborn NVP prophylaxis regimen to reduce perinatal HIV transmission *[9]*, NVP should only be used in combination with other antiretroviral drugs.

Adverse Effects

The most common adverse events reported in adults include skin rashes, elevation of serum transaminases, headache, nausea, and fever *[10-12]*. In initial clinical trials of NVP treatment in HIV-infected children, rash was observed in 24% *[13]*. When a 2-week lower dose "lead in" period was used, the incidence of rash was decreased *[1]*. In a study of 4-drug therapy including NVP (given with 2 week lower dose lead in), rash was observed in only 6% of children *[14]*. Granulocytopenia was the second most frequent adverse event, seen in 16% of children, but it should be noted the children were also receiving ZDV, a known cause of granulocytopenia *[1]*. In a retrospective analysis of 74 children treated with NVP in the United Kingdom, 20% developed rash despite a 2-week lower dose lead in period, although some children in this study received doses higher than those currently recommended *[15]*. However, only 4 children required cessation of treatment due to rash. By comparison, in a recent antiretroviral trial of infants and young children, only 3 of 52 infants developed grade 2 or greater rash *[14]*. Skin rash typically presents in the first 28 days after initiating therapy and in rare cases has progressed to Stevens-Johnson syndrome/toxic epidermal necrolysis, a severe skin rash accompanied by hypersensitivity reactions (characterized by rash; constitutional symptoms such as fever, arthralgia, myalgia, and lymphadenopathy; and visceral involvement such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction) or death. NVP should be permanently discontinued and not restarted if severe rash or rash with constitutional findings occurs. Patients experiencing rash during the two-week lead-in period should not have their NVP dose increased until the rash has resolved.

Liver function abnormalities and clinical hepatitis have been associated with NVP use. In HIV-infected adults treated with NVP, severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, have been reported (see **Matrix 1 in the Appendix**). In HIV-infected adults, risk factors for hepatic toxicity include elevated baseline serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 cell counts (particularly women with CD4 cell count >250/mm^3) *[11, 12, 16]*. However, serious liver dysfunction, while it can occur, appears much less common in pediatric patients receiving NVP therapy than in adults *[12]*.

The majority of cases of hepatic dysfunction in adults have occurred during the first 12 weeks of NVP therapy, and frequent and intensive clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure and, in some cases, death; patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis.

Pediatric Experience

NVP has been studied in HIV-infected children in combination with NRTIs or with NRTIs and a PI *[1, 14, 15, 17-20]*. Combination therapy with NVP, ZDV, and ddI in young infected infants was associated with sustained viral suppression in a small number of children *[17]*. A larger study, PACTG 356, treated infants and young children with three different NVP-containing regimens: ZDV/3TC/NVP, ZDV/3TC/ABC/NVP, or ZDV/3TC/NVP/NFV *[14]*. Twenty-four percent of 17 infants treated with the three drug regimen had viral suppression to <400 copies/mL HIV RNA, compared with 10 of 17 (41%) and 15 of18 (83%), respectively, of those treated with four drugs. Children who started therapy prior to 3 months of age had a better virologic outcome

compared with those starting at an older age (3.5 to24 months). PACTG 377 randomized 181 PI- and NNRTI-naïve mild-moderately immune suppressed children to one of four combination treatment regimens. All of the regimens contained d4T and a PI (either RTV or NFV); three of the four regimens also included NVP as part of combination therapy. Children in the NVP-containing arms experienced moderate or worse skin rash more frequently than those not receiving NVP. Those children receiving a four drug regimen containing both NVP and a PI had a significantly greater increase in CD4 cell count from baseline to week 24 then those receiving other regimens *[18]*.

Dosing recommendations for chronic treatment of children are somewhat controversial. Body surface area has traditionally been used to guide NVP dosing for infants and young children, with dosing recommended at 120 to 200 mg per meter^2 of body surface area every 12 hours, at a maximum of 200 mg per dose. Younger children (e.g., age < 8 years) may require the higher range of dosage (i.e., 200 mg per meter^2 of body surface area twice daily) *[17, 19]*. The drug label also includes dosing recommendations based on mg/kg dosing, with 7 mg/kg every 12 hours recommended for children aged < 8 years and 4 mg/kg every 12 hours recommended for children aged > 8 years, with a maximum dose of 200 mg. NVP apparent clearance adjusted for body weight is approximately two-fold greater in children under age 8 years; however, these clearance changes are gradual and the mg/kg dosing recommendations result in an abrupt 43% decrease in dose size when the 8th birthday is reached. Thus, many clinicians prefer the mg per meter^2 of body surface area dosing that was used in clinical trials, particularly for children around the eighth birthday.

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Protease Inhibitors

Amprenavir (APV, Agenerase®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Amprenavir (APV) was approved in April 1999 for use in combination with other antiretrovirals in adults and children 4 years of age and older. This approval was based on results of controlled trials in treatment-naïve and -experienced adults for up to 24 weeks. Pediatric approval was based on analysis of two open label trials in treatment-experienced children, one after 8 weeks of therapy and one after 4 weeks of therapy. APV has been available in both liquid and solid formulations, but manufacture of the 150 mg capsules was discontinued after December 2004. Fosamprenavir (f-APV), which is a prodrug of APV, was approved for use in adults in 2003. Currently only the 700 mg f-APV tablets are available, but this product has largely replaced the use of APV 150 mg capsules in adults, reducing the pill burden of eight APV capsules to one f-APV tablet twice daily in combination with other antiretroviral agents. Currently, f-APV tablets and an investigational oral suspension are under investigation in pediatric patients.

Approximately 90% of APV is protein bound, primarily by alpha$_1$-acid glycoprotein (AAG) and, to a lesser extent, albumin. AAG levels may vary significantly by ethnicity, age, HIV serostatus, and weight *[1]*. Like other agents in this class, APV is metabolized by cytochrome P450 isoenzyme CYP3A4 and, to a lesser extent, CYP3A5 and CYP2C9 *[2]*; there is potential for multiple drug interactions (see product label). Although the absolute bioavailability of APV has not been determined, the APV solution was found to be 14% less bioavailable than the capsule formulation, and therefore the two formulations are not interchangeable.

Resistance
APV therapy induces mutations in the HIV-1 protease gene at codons 46, 47, 50, 54, and 84 and at the p1/p6 cleavage site. At least two to three mutations are required at amino acid residues 46, 47, and 50 to produce >10-fold decrease in sensitivity. IDV or RTV-resistant virus is likely to be resistant to APV.

Adverse Effects
Data compiled from 30 phase I – III studies of APV in 1330 adult and pediatric patients revealed the following most frequently reported adverse events: nausea, diarrhea, rash, headache, oral paresthesia, and fatigue. The majority of adverse events were mild to moderate. Nausea, rash (including Stevens-Johnson syndrome), and vomiting were the most common adverse events associated with discontinuation of treatment *[1]*. The most common drug related adverse events in trials of pediatric patients were vomiting, nausea, diarrhea, and rash *[2]*. APV should be discontinued for severe rash, including Stevens-Johnson syndrome, or moderate rash with systemic symptoms. Signs of lipodystrophy have also been reported in a few patients on APV. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur. APV is related to the sulfonamides; however, the potential for cross-sensitivity between sulfonamides and APV is unknown. APV should therefore be used with caution in patients with sulfonamide allergy.

The FDA approved formulation of APV contains 46 IU of vitamin E/mL of oral solution. The recommended dose of APV results in a dose of 138 IU/kg/day of vitamin E using the oral solution. The Reference Daily Intake for vitamin E is 30 IU per day for adults and approximately 10 IU per day for children. There are few data regarding the use of extremely high-doses of vitamin E on a chronic daily basis. In a study using high-dose vitamin E in

premature infants, 20% of infants with high vitamin E serum levels had an increased incidence of bacterial sepsis and necrotizing enterocolitis *[3]*. Excess ingestion or administration of vitamin E in adults and animals has been associated with creatinuria, decreased platelet aggregation, impaired wound healing, prolongation of prothrombin time, hepatomegaly, and the potentiation of vitamin K deficiency coagulopathy. Adult and pediatric patients receiving APV should be advised not to take supplemental vitamin E.

The FDA approved liquid formulation of APV contains 550 mg of propylene glycol per mL, a concentration that exceeds WHO standards (25 mg/kg/day) for use in infants as food additive [17th Report of the Joint FAO/WHO Expert Committee on Food Additives 1974] (see **Matrix 1 in the Appendix**). Young infants have immature levels of alcohol dehydrogenase enzymes, which are involved in the metabolism of propylene glycol. There is concern that the propylene glycol contained in the liquid formulation may not be metabolized adequately and could cause toxicity. High levels of propylene glycol have been associated with hyperosmolality, lactic acidosis, seizures, and respiratory depression. Therefore, APV should not be used in its current liquid formulation in children under the age of 4 years. A new oral suspension of f-APV that does not contain large amounts of propylene glycol is currently under investigation.

Pediatric Experience
APV has been studied in HIV-infected children in combination with NRTIs *[4-8]*. In an open label, phase III study of 81 treatment-experienced children 3 to17 years of age receiving APV in combination with 2 NRTIs, 41% had plasma HIV RNA < 400 copies/mL and 65% had plasma HIV RNA < 10,000 copies/mL after 8 weeks of therapy. In this study, PI-naïve children had a greater antiviral response than PI-experienced children, with a median reduction in HIV RNA of 1.41 and 0.38 $\log_{10}$ copies/mL in PI-naive and PI-experienced children, respectively *[4]*.

f-APV has largely replaced APV capsules for use in adults because of the decrease in pill burden and absence of large amounts of vitamin E in the new tablet formulation. There are currently ongoing clinical trials of f-APV tablets in older children and an investigational oral suspension in pediatric patients.

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Atazanavir (ATV, Reyataz™)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Atazanavir (ATV) was approved in June 2003 for treatment of HIV infection in individuals over 16 years of age. Unlike other PIs, minimal effect on lipid levels has been observed in adults treated with ATV *[1]*. Safety and effectiveness of ATV in pediatric patients is under study, but an appropriate dosage has not yet been determined.

ATV is an azapeptide aspartyl PI that differs structurally from other approved peptidomimetic protease inhibitors. ATV is rapidly absorbed following oral administration, and should be administered with food to increase bioavailability and reduce pharmacokinetic variability. Administration with a light meal resulted in a 70% increase in systemic ATV exposure (AUC) and a 57% increase in peak levels relative to the fasting state, and administration with a high-fat meal resulted in a mean increase in AUC of 35% and no change in peak levels relative to the fasting state. ATV is extensively metabolized via the hepatic CYP3A enzyme pathway, and is primarily excreted in the feces in the form of metabolites. The median half-life in adults is 6.5 hours, allowing once daily administration. Passage into CSF is limited; in a multiple-dose study in HIV infected patients, the CSF-to-plasma ratio for ATV ranged between 0.0021 and 0.0026.

Resistance
Like other PIs, several mutations are generally required to result in clinically significant drug resistance *[2]*. ATV has a unique resistance profile. Treatment naïve patients developed a characteristic I50L mutation that is associated with increased susceptibility to other PIs; however, the clinical significance of this finding is unknown *[3]*. The I50L mutation is frequently detected in tandem with the A71V substitution *[3]*. In contrast, treatment experienced patients did not develop the I50L mutation; rather, these patients developed mutations (M46I, A71V/T, I84V, N88S/D, and L90M) that reduced response to ATV and conferred high level cross-resistance to other PIs. Generally, if there were pre-existing PI mutations in the patient's virus population prior to ATV initiation, ATV resistance developed through mutations associated with resistance to other PIs, instead of through the I50L mutation. While HIV isolates resistant to only one or two PIs may remain sensitive to ATV, cross-resistance with ATV increases as isolates exhibit increasing resistance to multiple PIs.

Adverse Effects
The most common side effects associated with ATV include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), headache, rash, tingling in hands and feet, and depression. Unlike other PIs, ATV does not appear to be associated with an increase in total cholesterol, LDL cholesterol, and triglycerides. As with other PIs, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

ATV inhibits the hepatic glucuronidation enzyme uridine diphosphate glucuronosyl transferase (UGT1A1) that conjugates bilirubin. ATV administration is frequently associated with asymptomatic indirect hyperbilirubinemia, which may be accompanied by scleral icterus or visible jaundice. This is not accompanied by elevations in hepatic transaminase levels, but may be cosmetically disturbing. The jaundice is reversible following discontinuation of ATV therapy. ATV has been reported to prolong the PR interval of the electrocardiogram. In the majority of patients, abnormalities in atrio-ventricular (AV) conduction were asymptomatic and limited to first-degree AV block; no second or third degree AV block has been observed. However, because experience with ATV is limited, caution should be exercised when ATV is used in patients with pre-existing conduction system disease or those receiving other drugs that prolong the PR interval (e.g., most beta-blockers, digoxin, verapamil).

ATV is principally metabolized by the liver, and individuals with hepatic impairment may have increased ATV concentrations. Individuals with hepatitis B or C infections or marked elevations in transaminases prior to treatment may be at increased risk for further elevations in transaminases or hepatic decompensation.

Pediatric Experience
ATV has been studied in HIV-infected children in combination with NRTIs and with low-dose RTV boosting *[4, 5]*. ATV pharmacokinetics, safety, and preliminary efficacy are being studied in a phase II study, PACTG 1020A, in HIV-infected children 3 months to 21 years of age. In addition to capsules, a powder formulation is also being evaluated.

ATV is not currently approved for use in children, but clinical trials are underway. Children may require higher doses than adults, and dose-finding studies are ongoing to determine the optimal dosage. To increase drug exposure, the use of ATV with a low-dose RTV boost is also being evaluated in children *[5]*. These pediatric dose-finding trials are using ATV plasma concentration monitoring to guide therapy. Appropriate pediatric dosing is unknown at this time. While ATV is approved for adolescents 16 years of age and older, adequacy of the adult dose for adolescents is not established;

low-dose RTV boosting may be required in adolescents.

Current recommendations for HIV-infected adults include the use of unboosted ATV only in treatment naïve patients. All treatment experienced patients should receive RTV-boosted ATV therapy. Decreased ATV exposure has been observed when co-administered with EFV and TDF; coadministration of ATV with low-dose RTV boosting is recommended if ATV is administered with either of these drugs.

No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving ATV in combination with 2 NRTIs *[4]*.

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Fosamprenavir (f-APV, Lexiva™)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview

In October 2003, fosamprenavir calcium (f-APV), a prodrug of amprenavir (APV), was approved for use in combination with other antiretrovirals for the treatment of HIV infection in adults. This approval was based on results from two studies in antiretroviral naïve adults and one study in PI-experienced adults. Pediatric trials are ongoing at this time.

The prodrug f-APV is rapidly and almost completely hydrolyzed to APV by cellular phosphatases in the gut as it is absorbed *[1, 2]*. The drug can be administered with or without food without any significant effects on pharmacokinetic parameters. Peak APV serum concentrations are reached between 1.5 and 4 hours (mean 2.5 hours). Approximately 90% of APV is plasma protein bound, primarily by alpha 1-acid glycoprotein (AAG). APV is extensively metabolized by cytochrome P450 isoenzyme CYP3A4; there is potential for multiple drug interactions. RTV inhibits the metabolism of APV, resulting in increases in both AUC and trough drug concentrations of APV. f-APV has not been studied in patients with hepatic insufficiency, but these patients may require a dose reduction. Unlike APV, the f-APV formulation contains no vitamin E.

Resistance

Genotypic analysis of isolates from APV-treated patients shows that mutations are induced in the HIV protease gene at codons 32, 46, 47, 50, 54, 84 and at the p1/p6 cleavage site. At least two to three mutations are required at amino acid resides 46, 47, and 50 to produce > 10-fold decrease in sensitivity. Varying degrees of cross-resistance among HIV-1 PIs have been observed.

Adverse Effects

f-APV is generally well tolerated. The most common side effects associated with f-APV include gastrointestinal symptoms (nausea, vomiting, diarrhea), perioral paresthesias, headache, and rash. When compared to NFV, there is a lower rate of gastrointestinal adverse effects. Although rash was reported in approximately 19% of patients in the efficacy trials, life-threatening rash, including

Stevens-Johnson syndrome, are rare, reported in < 1% of patients *[3, 4]*. f-APV should be discontinued for severe rash, including Steven-Johnson syndrome or moderate rash with systemic symptoms. APV is related to the sulfonamides, and the potential for cross-sensitivity of sulfonamides and APV is unknown. f-APV should therefore be used with caution in patients with a history of sulfonamide allergy. Fat redistribution and lipid abnormalities have been reported with the use of f-APV. As with other PIs, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and spontaneous bleeding in hemophiliacs may occur.

Pediatric Experience
Currently, f-APV is not approved for use in HIV-infected children. The drug is being studied in combination with NRTIs and the PI RTV *[3, 4]*. A multicenter, international study of the use of f-APV plus RTV is currently underway in pediatric patients using both the 700 mg tablets and an investigational suspension *[4]*. Both once daily and twice daily administration is being investigated in treatment naïve and PI experienced children.

The approved adolescent/adult dosing regimen depends on whether the patient is antiretroviral naïve or experienced. Only antiretroviral naïve patients should receive unboosted f-APV or once daily therapy. PI experienced patients should receive the RTV-boosted twice daily regimen.

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Indinavir (IDV, Crixivan®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Indinavir (IDV) was approved in 1996 for use in adults and adolescents older than 18 years. Like the other PIs, IDV is prone to multiple drug interactions due to its interaction with the cytochrome P450 system (see product label). A liquid formulation is not available. Administration of IDV with a meal high in calories, fat, and protein results in a reduction in plasma IDV concentrations; administration with lighter meals (e.g., dry toast with jelly, apple juice, and coffee with skim milk and sugar) results in little to no change in IDV pharmacokinetics. Decreased IDV exposure over time in children maintained on relatively fixed doses of IDV are associated with virological failure. This may be prevented by frequent dosage adjustment and therapeutic drug monitoring, when possible *[1]*.

Resistance
Resistance to IDV is associated with mutations at codons 10, 32, 54, 63, 71, 82, 84, and 90. Virus resistant to IDV may also be resistant to RTV. IDV-resistant virus may be broadly cross-resistant to all other PIs.

Adverse Effects
The most serious side effect observed in both adults and children is nephrolithiasis. In double-blind clinical trials in adults, the incidence of nephrolithiasis was 9.3% in IDV-containing treatment groups. Abnormal renal function (including acute renal failure) has been observed in a small number of patients with nephrolithiasis; abnormal renal function was generally transient and temporally related to the acute episode. Interstitial nephritis has also been observed in patients receiving IDV. If signs and symptoms such as flank pain with or without hematuria occur, temporary interruption of therapy (for 1 to 3 days) during the acute episode may be considered. Adequate hydration is essential when IDV is administered. Nephrolithiasis may be somewhat more frequent among children, likely due to the difficulty in maintaining adequate hydration; in an IDV study in 54 children, 13% developed hematuria *[2]*. Children treated with IDV also have a high cumulative incidence of sterile leukocyturia, which may be accompanied by elevations in serum creatinine in the absence of clinical symptoms of nephrolithiasis *[3]*.

Asymptomatic mild elevation of bilirubin, due to an increase in indirect bilirubin, has also been reported in adults and children receiving IDV. In adult trials, about 10% of IDV-receiving patients had bilirubin values ≥ 2.5 mg/dL at some point during treatment; in most cases, the maximum bilirubin elevations were observed after one or more weeks of treatment. Clinical adverse effects such as jaundice or elevations in serum transaminase levels have only rarely been reported. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported.

Pediatric Experience
IDV has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[1-14]*. IDV has been studied in small, uncontrolled pediatric trials, but has not been approved in the pediatric age group. IDV has been administered in dosage ranges of 300 to600 mg per meter^2 of body surface area given every 8 hours *[2, 4-10]*.

Virologic, immunologic, and clinical response to IDV-based therapy in children has been observed in several small studies. In an open label study in 28 children receiving IDV/ZDV/3TC, 70% of children had HIV RNA levels of < 500 copies/mL after 6 months of therapy *[8]*. In an open label study of IDV/d4T/3TC treatment in 25 Italian children, HIV RNA levels were maintained at < 400 copies/mL after 18 months of therapy in 87% of children who entered the study with CD4 cell counts in CDC Immune Class 2 and 72% of those who entered with CDC Immune Class 3 *[5]*. In a study in 33 infected children who had received ≥ 96 weeks of treatment with IDV/ZDV/3TC (with an initial 16 weeks of IDV monotherapy), a median increase in CD4 cell count of 199/mm^3 and a median decrease in HIV RNA of 0.74 log was observed at 96 weeks *[11]*. Virologic response in this study may have been impacted by the prolonged period of IDV monotherapy prior to combination with ZDV/3TC. In one study of 24 children receiving a regimen of IDV, ZDV, and 3TC, virologic responders showed significant increases in height and weight, but the virologic non-responders did not *[12]*. Finally, in another study of 21 children receiving PI-containing antiretroviral therapy, all patients receiving IDV experienced substantial increase in their triglyceride concentrations, but no significant increases in total cholesterol occurred; blood glucose concentrations were not significantly different between baseline and follow-up evaluations *[15]*.

Data in children indicate that a pediatric dose of 500 to 600 mg IDV per meter^2 of body surface area three times daily results in peak values similar to those in adults; however, there was a significant proportion of children whose trough IDV values were less than the 0.1 mg/L value associated with virologic efficacy in adults *[6]*. The more frequent incidence of renal toxicity in children than in adults has precluded studying higher doses of IDV *[2, 3]*. Therefore, two small studies have evaluated IDV in combination with low-dose RTV "boosting" in children. One study evaluated 500 mg IDV per meter^2 of body surface area plus 100 mg RTV per meter^2 of body surface area twice daily in 4 children aged 1 to10 years; in one child, this resulted in high concentrations of both drugs and was accompanied by symptoms of renal toxicity *[8]*. The other study evaluated 400 mg IDV per meter^2 of body surface area plus 125 mg RTV per meter^2 of body surface area twice daily in 14 children; this dosing resulted in AUC and trough levels similar to those observed with standard doses of IDV/RTV in adults (800 mg IDV/100 mg RTV twice daily), although the peak concentration was slightly decreased *[14]*. The rate of renal toxicity was 9%, no higher than observed in studies of IDV therapy alone *[2, 3, 14]*.

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Lopinavir/Ritonavir (LPV/RTV, Kaletra™)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Lopinavir/Ritonavir (LPV/RTV) is a fixed combination of two PIs: 133.3 mg of LPV plus 33.3 mg of RTV. LPV/RTV received FDA approval in 2000 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older. It is available in both liquid and capsule formulations. A new tablet formulation (200 mg LPV/50 mg RTV) that does not require refrigeration and can be administered without regard to food was approved on October 28, 2005.

Like other PIs, LPV/RTV is metabolized by the hepatic cytochrome P450 system and multiple drug interactions are possible (see product label). Administration of LPV/RTV with food increases plasma concentrations; to enhance bioavailability and minimize pharmacokinetic variability, LPV/RTV capsules and oral solution should be taken with food; LPV/RTV tablets can be administered without regard to food.

Recently, the FDA approved the use of LPV/RTV 800/200 mg once daily administration for the treatment of HIV infection in therapy naïve adults over age 18 years. Once daily administration has not been evaluated in pediatric or adolescent patients. Therapy experienced patients should only receive the twice daily regimen because trough concentrations are significantly lower with once daily administration, and there are no clinical trials comparing the two dosages in these patients. LPV/RTV should not be administered once daily in combination with EFV, NVP, APV, NFV, or other medications that could potentially further reduce LPV concentrations.

Resistance
Resistance to LPV/RTV has been associated with the accumulation of specific mutations in the protease enzyme; when compared to LPV susceptibility in wild type HIV-1, greater than 5-fold LPV resistance is found in the presence of one or more primary mutations at protease amino acid position 32, 47, 48, 50, 82, or 84 when that mutation is combined with three or more secondary mutations *[1, 2]*. In one study, virologic response to therapy, measured as HIV RNA < 50 copies/mL at 48 weeks, was associated with LPV susceptibility at the start of treatment, and virologic response rates of 81%, 60%,

and 25% were associated with baseline LPV phenotype susceptibility (defined as the fold-change in susceptibility compared to wild type HIV-1) of < 10-fold, > 10- to < 40-fold, and > 40-fold, respectively *[2]*. Similarly, treatment response was 83% and 52% when the number of baseline protease mutations was $\leq$ 5 or > 5, respectively.

More important than resistance alone is the relationship of the drug exposure (trough plasma concentration measured just prior to a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (50% effective concentration, or EC_{50}). The ratio of C_{trough} to EC_{50} is called the inhibitory quotient, and in both adults and children treated with LPV/RTV, virus load reduction is more closely associated with inhibitory quotient than with either the C_{trough} or EC_{50} alone *[3-5]*. Cross-resistance among PIs can occur. In patients failing therapy with LPV/RTV, detection of LPV resistance is more likely in patients with prior PI treatment compared to patients not previously treated with PIs.

Adverse Effects
The most common side effects associated with LPV/RTV have been diarrhea, asthenia, and triglyceride and cholesterol elevations. Pancreatitis has been reported in adult patients taking LPV/RTV. High triglyceride levels may be a risk factor for pancreatitis. As with all PI drugs, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

Pediatric Experience
LPV/RTV has been studied in HIV-infected children in combination with NRTIs and NNRTIs *[5-12]*. The use of dual PIs that include RTV have been studied in adults. In these combinations, rather than being used for its antiretroviral activity, RTV acts as a pharmacokinetic enhancer by inhibiting the metabolism of other PIs and therefore increasing their plasma concentrations. RTV inhibits the metabolism of LPV and thus increases its plasma concentration. Data on combination PIs in children is more limited.

Abbott Laboratories Study M98-940 was a Phase I/II open label study that evaluated the pharmacokinetic profile, tolerability, safety, and efficacy of LPV/RTV oral solution and either two NRTIs or NVP plus up to two NRTIs in 100 pediatric patients. Through 48 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/mL was 37 of 44 (84%) for antiretroviral naïve patients and 42 of56 (75%) for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral naïve and 284 cells/mm^3 for antiretroviral experienced patients treated through 48 weeks. In patients with viral load > 400 copies/mL at 24 or 48 weeks, there were no detectable changes in phenotypic susceptibility to LPV compared to baseline isolates, although there were resistance mutations to NRTIs and NNRTIs identified in the rebound isolates.

There is still some controversy about dosing of LPV/RTV in children. Children have much lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The "directly scaled" dose approximation of the adult dose in children can be calculated by dividing the adult dose by the usual adult body surface area of 1.73 $meter^2$. This suggests that for the adult dose of 400 mg LPV/100 mg RTV, the appropriate pediatric dose would be approximately 230 mg LPV/57.5 mg RTV per $meter^2$ of body surface area. However, for 12 children receiving 230 mg LPV/57.5 mg RTV per $meter^2$ of body surface area twice daily (without NVP), the mean C_{trough} was 4.74 $\pm$ 2.93 mcg/mL (about 67% of the adult value, which was 7.1 $\pm$ 2.9 mcg/mL) *[6]*. To achieve similar C_{trough} to that observed in adults at the standard dose, the pediatric dose would need to be increased 30% over the directly body surface area-scaled dose. For 15 children treated with 300 mg LPV/75 mg RTV per $meter^2$ of body surface area twice daily (without NVP), the mean C_{trough} was 7.91 $\pm$ 4.52 mcg/mL, similar to that in adults treated with 400 mg LPV/100 mg RTV mg twice daily.

For children, as in adults, the LPV C_{trough} is further reduced by concurrent treatment with NVP, and in 14 children treated with 230 mg LPV/57.5 mg RTV per $meter^2$ of body surface area twice daily plus NVP, the mean C_{trough} was 3.77 $\pm$ 3.57 mcg/mL *[6]*. For 12 children treated with 300 mg LPV/75 mg RTV per $meter^2$ of body surface area twice daily, the mean C_{trough} was 5.62 $\pm$ 3.32 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/RTV, the variability in concentration is much higher in children than adults *[6]*.

A pilot observational study using the inhibitory quotient (the ratio of C_{trough} to EC_{50}) to guide therapy and evaluate the benefit and safety of higher doses

of LPV/RTV in 12 children failing prior antiretroviral therapy has been conducted *[5]*. Studies of the practical application of the inhibitory quotient to guide therapy and of higher doses of LPV/RTV in children and adolescents are ongoing.

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Nelfinavir (NFV, Viracept®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Nelfinavir (NFV) is approved for use in children over 2 years of age in combination with NRTIs and NNRTIs. It is available in both oral powder and tablet formulations. NFV is active against both HIV-1 and HIV-2 strains.

In adults, exposure to NFV is significantly increased by administration with food. Compared to administration in the fasted state, adults administered NFV with a 500 Kcal meal with 20% fat have an AUC and peak level (C_{max}) increase of 3.1-fold and 2.5-fold, respectively. When given with 500 Kcal but 50% fat, AUC and C_{max} increase by 5.1-fold and 3.8-fold, respectively. Increasing the calories to 1000 Kcal and leaving the fat at 50% does not further increase these pharmacokinetic parameters (product label). Because of the large food effect seen with NFV administration, variations in plasma concentrations are likely to occur. Like other PIs, NFV is metabolized by the cytochrome P450 enzyme system in the liver, inhibits CYP3A4, and is associated with a number of clinically significant pharmacologic drug interactions.

Resistance
NFV-resistant virus contains a unique protease enzyme mutation at codon 30, which alone does not confer cross-resistance to other PIs, but does result in reduced replication capacity of the HIV isolate *[1]*. In adults, the mutation at position 30 occurs in approximately 30% of patients with virologic failure, while a mutation at amino acid 90 occurs in only about 5% *[2]*. Since the mutation at position 30

does not lead to cross-resistance to other PIs (unlike the mutation at position 90), some have suggested that NFV may be a good choice for use as the first PI in adults, since virologic failure accompanied by mutation at position 30 may not constrain future PI choice. However, in children failing NFV in their first PI-containing regimen, the mutation at position 30 occurred in 30% (similar to that in adults), but the mutation at position 90 was also relatively frequent, occurring in 24% of the 41 patients studied *[3]*. This may limit future therapeutic options for some children. Moreover, continued use of NFV in the presence of viremia may result in the selection of additional mutations in the protease gene at amino acid positions 30, 35, 36, 46, 48, 71, 77, 82, 84, 88, and 90, which leads to decreased susceptibility to other PIs. While changing from NFV to another PI may be effective if the mutation at position 90 or multiple other PI mutations have not developed, changing to NFV from another PI is less likely to be effective, since mutations selected for by other PIs confer high-level cross-resistance to NFV *[4]*.

Adverse Effects
NFV has been relatively well tolerated in children, even when dosing schemes exceed adult recommended amounts. The most common adverse effects include diarrhea, abdominal pain, flatulence, and rash. NFV causes a secretory diarrhea through a calcium-dependent process *[5]*; in adults, administration of calcium carbonate at the same time as NFV may reduce the diarrhea *[6]* without decreasing plasma concentrations of NFV or its major metabolite, M8 *[7]*. As with other PIs, new onset diabetes mellitus and exacerbations of previous hyperglycemia have been reported, as has the occurrence of the lipodystrophy syndrome.

Pediatric Experience
NFV has been studied in HIV-infected children in combination with other antiretroviral drugs *[8-24]*. In children between 2 and 13 years of age receiving NFV as part of triple antiretroviral therapy in randomized trials, the proportion of patients with HIV RNA < 400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26 to 69%. Response to NFV-based therapy has varied by antiretroviral experience, the number of drugs included in the combination regimen, age, and dose.

Better control of plasma viremia is observed in antiretroviral naïve than experienced children. In two small studies including 44 antiretroviral naïve children who received NFV in combination with two NRTI drugs, HIV RNA levels after 48 weeks of therapy were < 400 to 500 copies/mL in 56 to 69% (< 50 copies/mL in 44 to 48%) of children *[9, 10]*. In contrast, in PACTG 377, a study of antiretroviral experienced children, response rates to two NFV-containing triple therapy regimens (NFV plus d4T/3TC or d4T/NVP) in 94 children ranged between 30 to 42% after 48 weeks of therapy *[12]*.

Improved virologic response has been observed in antiretroviral experienced children when NFV is used as part of a four drug regimen. In two studies including 99 children who received NFV combined with 2 NRTIs plus an NNRTI, virologic response with HIV RNA < 400 copies/mL after 48 weeks of therapy was observed in 72% of children receiving EFV and 52% receiving NVP as the NNRTI *[11, 12]*.

Antiviral response in children under age 2 years is less than in older children. Agouron study 566 was a placebo-controlled trial of NFV in combination with ZDV/ddI in 141 minimally pretreated HIV-infected children. For the 94 children ages 2 to12 years of age, week 48 HIV RNA levels were < 400 copies/mL in 26%, compared to 2% of the 47 children under age 2 years. In a study of combination NFV-based therapy in 20 infants with median age of 2.5 months at time of therapy initiation, after 48 and 72 weeks of therapy HIV RNA was < 400 copies/mL in 37% and 44%, respectively, and < 50 copies/mL in 21% and 25% *[10]*.

As in antiretroviral experienced children, improved virologic response may be seen with NFV-based therapy when it is used as part of a four drug regimen in children aged over 2 years. In PACTG 356, children under age 2 years were treated with ZDV/3TC/NVP, ZDV/3TC/NVP/ABC, or d4T/3TC/NVP/NFV *[14]*. More children who received the NFV-based four 7drug regimen had HIV RNA levels < 400 copies/mL after 48 weeks of therapy than those treated with NRTI-based therapy: 83% of 18 children who received the NFV four drug regimen had HIV RNA < 400 copies/mL after 48 weeks of therapy, compared to 41% of 17 children who received ZDV/3TC/NVP/ABC and 24% of 17 children who received ZDV/3TC/NVP.

The relatively poor ability of NFV to control plasma viremia in infants and children may be related in part to its reduced potency compared to other PIs or NNRTIs, as shown by studies in adults and adolescents *[15, 25]*. However, a significant portion of the poor outcome with NFV in children may be

related to issues related to palatability of the powder formulation, or to pharmacokinetic differences of NFV in infants, children, adolescents, and adults *[16]*.

The pediatric formulation of NFV is a powder that results in a change in the consistency of food or formula to which it is added. This change in consistency makes this formulation of the drug unpalatable to some children, who may prefer the bitterness of the crushed tablets to the sandy consistency of food or formula containing NFV pediatric powder. In the PENTA-7 trial, 7 (35%) of the 20 infants who started therapy with the NFV powder switched to crushed tablets because of the difficulty of administering the powder to infants *[13]*.

Determining an appropriate and effective dose of NFV in children is complicated by highly variable drug pharmacokinetics, particularly in young infants. In children ages 2 to12 years, administration of NFV 30 mg/kg/dose three times daily achieves lower drug exposure than administration of 55 mg/kg/dose twice daily, and this difference is most marked in children weighing < 25 kg *[17]*. Children < 25 kg may have less than half the drug exposure than children > 25 kg when comparable body-weight-adjusted doses are used *[18]*. Moreover, the variability of drug exposure at any given dose is much higher for children than adults *[19]*, which has been attributed at least in part to differences in the diet between children and adults.

Infants have even lower drug exposure and higher variability in plasma concentrations than children < 25 kg, and the presence of lower peak drug levels and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be factors *[21, 26]*. Even with doses of 150 mg/kg/day (given two to three times daily), 16.7% of children had peak levels and 27.8% of children had 24 hour AUC that were below the 10th percentile of adult values *[22]*. While it is suggested that dosing in infants might improve if a mg per $meter^2$ of body surface area dosing regimen were used *[21, 23]*, such dosing is not recommended at this time.

Studies in adults and children have demonstrated an increased risk of virologic failure associated with low NFV drug exposure, particularly with a NFV C_{min} < 1.0 mcg/mL *[27-29]*. In a study of 32 children treated with NFV 90 mg/kg/day divided into two or three doses a day, 80% of those with morning trough NFV plasma concentration > 0.8 mcg/mL had week 48 HIV RNA levels < 50 copies/mL, compared to only 29% of those with morning trough < 0.8 mcg/mL *[30]*. It is of note that the median age of the group with C_{trough} < 0.8 mcg/mL was 3.8 years, while the median age of the group with C_{trough} > 0.8 mcg/mL was 8.3 years *[30]*.

Therapeutic drug monitoring of NFV plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with NFV *[27]*. In a study in adults with HIV infection, treatment was started at the standard adult dose of 1250 mg twice daily; low drug levels were treated first with a discussion of correct intake with food, and then with dosage increases to 1500 mg twice daily or 1750 mg twice daily *[31]*. Given the enhanced variability of NFV plasma concentrations in infants and children, benefits of therapeutic drug monitoring and appropriate dose adjustment might be even greater for children.

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Ritonavir (RTV, Norvir®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Ritonavir (RTV) is approved for use in children in combination with other antiretroviral agents and is available as liquid and capsule formulations. It has specific activity for HIV-1 and, to a lesser extent, HIV-2. RTV is a potent inhibitor of the cytochrome P450 enzyme pathway and significantly interferes with the metabolism of many medications, including macrolides and certain antihistamines (see **Matrices 2 – 4 in the Appendix** and the product label). Although RTV inhibits cytochrome P450 CYP3A, it induces its own metabolism. It is well absorbed, with a half-life of 2 to 4 hours in children *[1, 2]*. Pharmacokinetic studies in HIV-infected children 2 to14 years of age may indicate that while RTV clearance is similar to that seen in adults, variability in clearance is likely to be greater in children than in adults due to age-related changes in drug metabolism.

Resistance
The most significant genotypic resistance mutations associated with RTV are those found at protease codons 46, 82, 84, and 71. Multiple genotypic mutations are required for resistance to develop, although the 82 mutation appears to be necessary but not sufficient to confer phenotypic resistance. There is cross-resistance between RTV and IDV, and many isolates resistant to IDV may also be resistant to saquinavir. Use of one of these agents following the failure of another is not routinely recommended unless viral resistance status is known for the specific PI.

Adverse Effects
One small phase I study in children demonstrated a high rate of gastrointestinal intolerance with use of RTV *[1]*. However, larger studies have shown better tolerance of the drug, particularly when dose escalation is used when initiating therapy. In PACTG 338, approximately 80% of children were able to tolerate RTV at 24 weeks of therapy *[3]*. Circumoral paresthesia and taste perversion have been reported in adults receiving the drug. Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have been reported in adults receiving RTV alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevation in patients with hepatitis B or C virus infection. Caution should be exercised when administering RTV to patients with pre-existing liver disease.

Pediatric Experience
RTV has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[1-12]*. Data from several pediatric studies demonstrate that RTV appears safe and is associated with clinical and virologic response in children.

RTV was studied in combination with one or two NRTIs in children in PACTG 338; there was a mean decrease of > 1.5 log in viral RNA levels after 12 weeks of therapy *[4]*. After 48 weeks of RTV plus two NRTIs, 42% of children maintained HIV RNA levels below the limit of detection of the assay, compared with 27% of children receiving RTV plus only one NRTI. Another small study of PI naïve children receiving RTV with two NRTIs showed an increase of greater than 400 CD4 cells/mm^3 after 12 months of therapy *[5]*. PACTG Protocol 377 randomized antiretroviral experienced, PI and NNRTI naïve children to four different treatment regimens, including RTV/d4T/NVP. The median increase in CD4 cell count for those on this regimen was 254 cells/mm^{3,} and 41% of children had HIV RNA less than 400 copies/mL at 24 weeks of treatment *[6]*.

Several small studies in children suggest that, as in adults, RTV can be used as a pharmacokinetic enhancer in dual PI regimens. RTV acts by inhibiting the metabolism of the other PI, therefore increasing the plasma concentration of the second PI. For example, two small studies have evaluated use of low-dose RTV to increase levels of IDV in an every 12-hour dosing regimen in children *[7, 8]*. However, while these RTV-boosted PI regimens are promising, the appropriate dosing in children and adolescents is not known for the different possible PI combinations. Additional pharmacokinetic studies are necessary before more definitive dosing recommendations can be made.

Similar to other PIs, clearance of RTV is greater in young infants than in older children and adults.

Preliminary data from PACTG 345, which looked at RTV alone and in combination with 3TC and ZDV in children less then 2 years of age, showed that concentrations are highly variable, and doses of 350 to 450 mg/m^2 twice a day may not be sufficient for long-term suppression of viral replication in this age group *[9]*.

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Saquinavir (SQV, hard gel capsule, Invirase®; soft gel capsule, Fortovase®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview

In 1995, saquinavir (SQV) became the first PI approved for use in adults and adolescents older then 16 years in combination therapy with NRTIs. In its original formulation as a hard gel capsule (Invirase), it had very limited bioavailability (~ 4%) following oral administration. In 1997, the FDA approved a soft gel capsule preparation (Fortovase) with significantly enhanced oral bioavailability. Absorption of SQV soft gel capsule is enhanced by food. In 2003, the FDA approved Invirase for use in boosted dosing regimens with RTV, allowing for twice daily dosing. In early 2006, Fortovase will no longer be available because a 500 mg tablet of Invirase with RTV boosting affords fewer gastrointestinal side effects with lower pill burden. SQV has not been formally approved for use in children, and is not yet available in a liquid preparation.

SQV is more than 90% metabolized by cytochrome P450 3A4 isoenzymes, the same enzyme system which metabolizes RTV. RTV, NFV, and LPV/RTV have been shown to inhibit the metabolism of SQV; plasma levels of SQV are increased when it is co-

administered with these agents. As with the other PIs, multiple pharmacological interactions are possible with coadministered agents that are also metabolized by CYP3A4.

Resistance
Resistance to SQV is associated with a unique mutation pattern in the HIV protease gene, primarily in codons coding for amino acids at positions 48 and 90. Secondary mutations, which also contribute to resistance, may occur at amino acid positions 10, 54, 71, 73, 77, 82, and 84. Viral isolates resistant to SQV are not necessarily resistant to the other PIs. However, phenotypic resistance to NFV has been demonstrated following SQV use, despite the lack of the usual NFV resistance mutations (e.g., D30N), perhaps caused by the secondary resistance mutations sometimes selected for by SQV, especially at positions 54 and 82 *[1]*. Continued use of SQV without complete virologic suppression may lead to cross-resistance with other PIs due to the accumulation of secondary mutations. Viral isolates resistant to RTV and IDV are usually also resistant to SQV.

Adverse Effects
The drug is usually well tolerated; mild gastrointestinal disturbances (diarrhea, nausea, abdominal pain) and reversible elevations in liver function tests are the most common side effects reported in adults. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported with the use of SQV. Elevated cholesterol and triglyceride levels have been reported in some patients taking SQV in combination with RTV.

Pediatric Experience
SQV has been studied in HIV-infected children with NRTIs and other PIs *[2-6]*. The generally low bioavailability of both the hard gel and soft gel capsules of SQV has led to the recommendation in adults that SQV be administered with another PI; addition of the second PI would lead to a delay in SQV clearance and increase the SQV AUC and trough plasma concentrations. Such “SQV boosting” has been studied in adults using NFV, RTV, LPV/RTV, or ATZ as the second PI *[6-14]*.

Initial studies in children demonstrated that the pharmacokinetics of the soft gel formulation of SQV were different than that in adults; SQV administered as the sole PI resulted in levels much lower than observed in adults, and did not reliably provide effective plasma drug levels in children *[2, 3]*. In one study, children < 24 kg receiving a 50 mg/kg/dose every 8 hours had drug exposures similar to that in adults. However, children > 28 kg required approximately two-fold higher doses than the adult dose (1200 mg every 8 hours) to gain more acceptable SQV drug exposure *[4]*. Thus, combination of SQV with another PI that would increase drug exposure will also be required in children, but data on the appropriate drug doses for children are not yet available.

SQV in combination with NFV, RTV, or LPV/RTV has been studied in pediatric patients *[2-6]*. Administration of SQV in combination with NFV (33 mg/kg SQV and 30 mg/kg NFV, both given three times daily) resulted in increased SQV exposure in children to levels that approached those observed in adults *[4]*. In 13 children receiving this regimen, the median change in HIV RNA levels was 2.58 log copies/mL, with 62% of children having HIV RNA levels < 50 copies/mL at 48 weeks *[3]*. In a study of 23 pediatric patients, a significant correlation between average trough concentration and sustained viral suppression was observed, with an apparent threshold mean trough SQV concentration above 200 ng/mL correlating with sustained viral suppression *[4]*.

SQV has also been studied in children in combination with RTV; in six children (median age 9.5 years) treated with two NRTIs plus SQV plus RTV for salvage therapy (SQV 15 to 30 mg/kg/dose and RTV 250 to 400 mg/m^2/dose, both given twice daily), there was a drop in virus load of -1.4 log copies/mL by 6 months of therapy, but no patient achieved an undetectable viral load *[2]*. For seven children failing therapy with ZDV, ddI, and SQV hard gel capsules (Invirase 400 to 500 mg per meter^2 of body surface area given three times daily, maximum dose 600 mg three times daily), the addition of RTV 300 to 400 mg per meter^2 of body surface area given twice daily resulted in median change in viral load of –3.6 log copies/mL, with 5 out of 7 achieving HIV RNA < 400 copies/mL (and 3 out of 7 achieving < 50 copies/mL) *[5]*.

While these boosted PI regimens are promising, the appropriate dosing in children and adolescents for the different possible PI combinations is not known. Additional pharmacokinetic studies are necessary before more definitive dosing recommendations can be made.

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Tipranavir (TPV, Aptivus®)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview

Tipranavir (TPV) is a non-peptidic HIV-1 protease inhibitor. TPV co-administered with RTV was approved by the FDA in June 2005 for treatment of HIV-1 infection in adult patients who are highly treatment experienced or have HIV-1 strains resistant to multiple protease inhibitors, and who have evidence of viral replication. The indication and approval of TPV/RTV was based on analyses of HIV-1 RNA levels documented in 2 controlled studies (RESIST-1 and RESIST-2) of TPV/RTV given over 24 weeks to adults with clinically advanced disease and treatment experience with 3 classes (NRTI, NNRTI, and PI) of antiretroviral drugs *[1, 2]*. The risk/benefit of TPV/RTV has not yet been established in treatment naïve adult patients or in pediatric patients.

TPV must be co-administered with RTV to exert its therapeutic effect. TPV and RTV are not co-formulated and must be given twice daily as the two separate products. Failure to correctly co-administer TPV with RTV will result in plasma levels of TPV that are insufficient to achieve the desired antiviral effect and will alter some of the known drug-drug interactions.

Several clinically important points were identified in the review of the pivotal trials. The use of other active agents with TPV/RTV was associated with a greater likelihood of treatment response. Genotypic or phenotypic testing and treatment history should guide the use of TPV/RTV because the number of baseline primary PI mutations affects the virologic response (see below under “Resistance”).

Metabolism of TPV is complex. TPV is a CYP3A substrate, an inhibitor of multiple other cytochrome P450 enzymes, and a P-glycoprotein substrate and apparent inducer. When combined with RTV, the

net effect is CYP3A inhibition and P-gp induction. The extensive drug-drug interaction potential of TPV/RTV when co-administered with multiple classes of drugs must be considered prior to and during use of TPV/RTV.

Resistance
Analyses of HIV-1 genotypes in heavily treatment experienced adults demonstrated that mutations at 16 amino acid codons of the protease gene were associated with reduced susceptibility to TPV: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. In the pivotal trials (RESIST-1 and RESIST-2), response to TPV/RTV decreased with increasing numbers of protease mutations. Response rates were reduced if $\geq$ 5 PI-associated mutations were present at baseline and if subjects did not receive concomitant enfuvirtide (T-20). TPV/RTV was associated with better virologic responses in patients with similar numbers of baseline PI mutations than the responses to the comparator PI/RTV *[3]*.

Adverse Effects
In adult patients, the most commonly reported adverse effects observed with the use of TPV/RTV included diarrhea, nausea, fatigue, headache, and vomiting. Mild to moderate rashes have been reported in subjects receiving TPV/RTV, and were reported in more female than male patients. In one drug interaction study of TPV/RTV with oral ethinyl estradiol, 33% of healthy female volunteers developed rash. TPV contains a sulfa moiety and should be used with caution in patients with known sulfonamide allergy.

Treatment with TPV/RTV has been associated with large increases in total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed prior to initiating TPV/RTV and at periodic intervals during therapy.

TPV/RTV has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. For all patients, liver function tests should be performed at initiation of treatment with TPV/RTV and monitored frequently throughout treatment. Patients with chronic hepatitis B or hepatitis C co-infection are at increased risk for developing worsening transaminase elevations or hepatic decompensation and warrant extra vigilance. TPV is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C).

Pediatric Experience
There are no published data on the safety or efficacy of TPV/RTV in pediatric patients, and there are insufficient pharmacokinetic data to recommend a pediatric dose. An oral liquid formulation is under investigation. One pediatric study enrolling children between 2 and 18 years of age is currently ongoing and will evaluate two doses of TPV/RTV in combination with background therapy over 48 weeks.

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Fusion Inhibitors

Enfuvirtide (Fuzeon™, T-20)

URL:**http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**
See Also: **Appendix: Characteristics of Available Antiretroviral Drugs**

Overview
Enfuvirtide (T-20) was approved in March 2003 for HIV-infected adults and children 6 years or older for use in combination with other antiretroviral drugs for the treatment of HIV infection in treatment experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. T-20 is a novel, synthetic, 36 amino acid peptide that binds to a region of the HIV envelope glycoprotein gp41; this binding prevents fusion of the virus envelope with the membrane of the CD4 host cell. It is a potent and selective inhibitor of HIV-1 entry in vitro, and has induced virologic responses in phase III clinical trials in adults and in phase I/II trials in children *[1-3]*. T-20 comes as a sterile powder that must be reconstituted with sterile water and administered by subcutaneous injection. Each injection should be given at a site different from the preceding injection site, and should not be injected into moles, scar tissue, bruises, or the navel. T-20 is approximately 92% protein bound, predominantly to albumin. As a peptide, T-20 undergoes catabolism to its constituent amino acids, with subsequent

recycling of the amino acids into the general body pool. T-20 does not affect the metabolism of drugs metabolized by liver CYP450 enzymes.

Resistance
Clinical isolates of HIV that are resistant to NRTIs, NNRTIs, and PIs remain susceptible to T-20 in cell culture. However, HIV isolates with reduced susceptibility to T-20 have been selected in vitro, although primary resistance to T-20 in treatment naïve patients is very rare *[4]*. The results from in vitro studies indicate that two amino acid substitutions (G36S and V38M) within the HR1 region of the HIV gp41 glycoprotein can lead to T-20 resistance *[5]*. In clinical trials in adults, HIV isolates with reduced susceptibility to T-20 have been recovered, demonstrating that HIV quasispecies in infected patients can undergo in vivo selection of resistant variants as a result of T-20 therapy. Decreases in susceptibility ranging from 4- to 422-fold relative to baseline virus have been observed with genotypic changes in gp41 amino acids 36 to 45. Antibodies to HIV-1 gp41 that are cross-reactive to T-20 do not appear to decrease the clinical efficacy of enfuvirtide *[6]*.

Adverse Effects
Local injection site reactions are common, occurring in 98% of adults, although only 3% required T-20 discontinuation. Symptoms included pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Although infection is uncommon (1% of patients), caregivers should monitor injection sites carefully for signs or symptoms of cellulitis or local infection. Biopsies of local cutaneous reactions indicated a variety of pathologies, including a chronic scleroderma-like pathology, suggesting that injection sites should be rotated *[7]*. An increased rate of bacterial pneumonia (4.7 pneumonia events per 100 patient-years) was observed in T-20 – treated adults in phase III studies compared to the control arm; the relation of this finding to T-20 use is uncertain. However, patients should be monitored for signs and symptoms of pneumonia, particularly if they have a low initial CD4 cell count, high initial viral load, history of prior lung disease, or are intravenous drug users or smokers (a particular concern in adolescents). Other adverse events reported in trials include insomnia, myalgia, peripheral neuropathy, and depression.

Serious hypersensitivity reactions are rare. Symptoms include rash, fever, nausea and vomiting, chills, hypotension, and elevated liver transaminases; other presumably immune-mediated symptoms include respiratory distress, glomerulonephritis with hematuria, and Guillain-Barre syndrome. If such symptoms occur, therapy with T-20 should be discontinued and should not be restarted, as hypersensitivity may recur on rechallenge. Treatment-related eosinophilia occurred in 11.2% of adults in a phase III trial, compared to only 2.4% of control patients *[1]*. However, eosinophilia was not associated with clinical events suggestive of systemic hypersensitivity.

In a trial of chronic T-20 in 14 children (see below), no life-threatening adverse events were identified, and no systemic serious toxicities were related to T-20 administration. Six wheezing episodes were noted in 4 children, and one episode of bacteremia was identified, but none were judged related to T-20. As in adult trials, injection site reactions were frequent, observed in 79% of children, but were generally mild *[2]*.

Pediatric Experience
T-20 has been studied in HIV-infected children in combination with other antiretroviral drugs *[2, 3, 8-10]*. PACTG 1005 initially studied T-20 in 14 HIV-infected children aged 4 to 12 years with incomplete viral suppression on their current antiretroviral regimen (plasma HIV RNA levels > 10,000 copies/mL while receiving a stable combination of 2 NRTIs plus an NNRTI or a PI for at least 16 weeks) *[2]*. Part A included a single-dose pharmacokinetic evaluation of T-20 given subcutaneously and then intravenously at 15, 30, or 60 mg per meter^2 of body surface area. The dose of T-20 that reliably resulted in the target trough concentration (1,000 ng/mL) was 60 mg per meter^2 of body surface area per dose, the approximate "equivalent" of a 90 mg dose delivered to a typical adult with a body surface area of 1.7 meter^2. This resulted in the recommended pediatric label dose in children aged 6 to 16 years of 2 mg/kg (maximum 90 mg) twice daily administered subcutaneously. In a second pediatric study of 18 children aged 6 to 16 years, the 2 mg/kg dose was found to yield drug concentrations similar to the 60 mg per meter^2 of body surface area dose. Further data are needed in children less than 6 years of age. No metabolic induction or inhibition of T-20 was observed in PACTG 1005, nor was there a statistical relationship, within the utilized dosing schedule, between drug exposure with this agent and virologic benefit *[8]*.

Part B of PACTG 1005 evaluated the safety and antiretroviral activity of chronic twice daily subcutaneous T-20 administration at 60 mg per meter^2 of body surface area per dose. For 7 days, the drug was added to each child's background antiretroviral regimen; at day 7, each child's background therapy was changed to a regimen that was predicted to be virologically active, while T-20 was continued. Children were followed for up to 96 weeks on the study. Two elected to discontinue T-20 within 24 weeks (one due to injection aversion, one due to a surgical procedure), 4 discontinued due to virologic failure (defined as > 1 log increase in viral load above baseline), and 2 discontinued due to Grade 3 toxicity. In this cohort, most children had local injection site reactions. 79% of children had > 0.7 log reduction in HIV RNA by day 7. At 24 weeks of treatment, 71% had a > 1.0 log reduction, 43% were suppressed to < 400 copies/mL, and 21% were suppressed to < 50 copies/mL *[3]*. However, only 36% of children maintained virologic suppression (> 1.0 log decrease in HIV RNA) at week 96 *[9]*. Significant improvements in CD4 percentage and height z-score were observed in children receiving T-20 for 48 and 96 weeks.

T20-310, a phase I/II study of T-20 (2.0 mg/kg subcutaneously, maximum 90 mg, twice daily) plus optimized background antiretroviral agents, enrolled children 3 to 16 years of age. A 24 week subanalysis comprising 28 enrolled adolescents (12 to 16 years of age) was performed. Twenty completed 24 weeks of therapy and 7 discontinued for non-safety reasons; questionnaires and returned unused T-20 vials demonstrated that approximately 50% were < 80% adherent with T-20 dosing. In those treated for 24 weeks, the median viral load decreased 0.59 log copies/mL, and there was a median increase in CD4 parameters: an absolute increase of 139 cells/mm^3 and an increase in CD4% of 4.9 to 15.1. Overall, only 3 of 28 enrolled adolescents had a viral load < 400 copies/mL at 24 weeks *[10]*.

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